

Original Article

Zoledronic acid improves periodontal health, reduces serum inflammation, and enhances bone metabolism in postmenopausal osteoporosis complicated by periodontitis

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Received September 20, 2024; Accepted November 1, 2024; Epub November 15, 2024; Published November 30, 2024

Abstract: Objective: To investigate the effects of zoledronic acid (ZA) on periodontal indices, serum inflammatory markers, and bone metabolism in postmenopausal osteoporosis (PMO) patients with periodontitis (PD). Methods: A total of 113 PMO+PD cases were recruited between May 2021 and February 2024. Fifty-two cases in the control group received standard therapy, while 61 cases in the observation group were treated with ZA. Therapeutic efficacy, periodontal indices (attachment loss [AL], probing depth [PD], and gingival bleeding index [GBI]), serum inflammatory markers (interleukin-1 β [IL-1 β], tumor necrosis factor- α [TNF- α], and C-reactive protein [CRP]), bone metabolism markers (N-terminal midfragment of osteocalcin [N-MID], beta-CrossLaps [β -CTx], and human calcitonin [hCT]), safety (fever, constipation, muscle soreness), and bone mineral density (BMD) at the lumbar spine and proximal femur were analyzed. A multivariable binary logistic regression model was used to determine factors influencing therapeutic efficacy. Results: The observation group demonstrated significantly better therapeutic outcomes than the control group. Treatment type was identified as an independent factor influencing efficacy. In the observation group, AL, PD, GBI, IL-1 β , TNF- α , CRP, N-MID, and β -CTX levels were significantly reduced post-intervention compared to pre-intervention levels and the control group (all $P < 0.05$), with no significant inter-group differences in hCT levels or adverse event rates (both $P > 0.05$). BMD in the lumbar spine and proximal femur improved significantly in the observation group compared to the control group (both $P < 0.05$). Conclusions: ZA positively impacts periodontal health, reduces serum inflammation, and enhances bone metabolism in PMO patients with PD.

Keywords: Zoledronic acid, postmenopausal osteoporosis, periodontitis, periodontal indices

Introduction

Postmenopausal osteoporosis (PMO) is a metabolic disorder primarily linked to estrogen deficiency, a steroid hormone that declines with age as ovarian function ceases [1, 2]. This deficiency increases fracture risk and is associated with higher mortality rates and economic burdens [3]. Statistics indicate that nearly one-third of women over 50 are affected by osteoporosis (OP), and women across all age groups exhibit significantly lower bone mass compared to men of the same age and race [4, 5].

Periodontitis (PD) and OP are both skeletal diseases closely related to inflammation and

aging. PD involves chronic inflammation of periodontal tissue and alveolar bone, leading to gingival sulcus deepening, as well as plaque and tartar accumulation [6]. Studies have shown a clinical link between PD and OP, suggesting that systemic and alveolar bone loss may contribute to this correlation [7]. However, research on treating PMO complicated by PD is limited, focusing mainly on the relationship between PMO and PD or the effects of ZA on either condition individually. This study aims to address this gap by providing relevant analyses and further clinical insights.

Zoledronic acid (ZA), typically administered intravenously, is widely used to treat OP, helping

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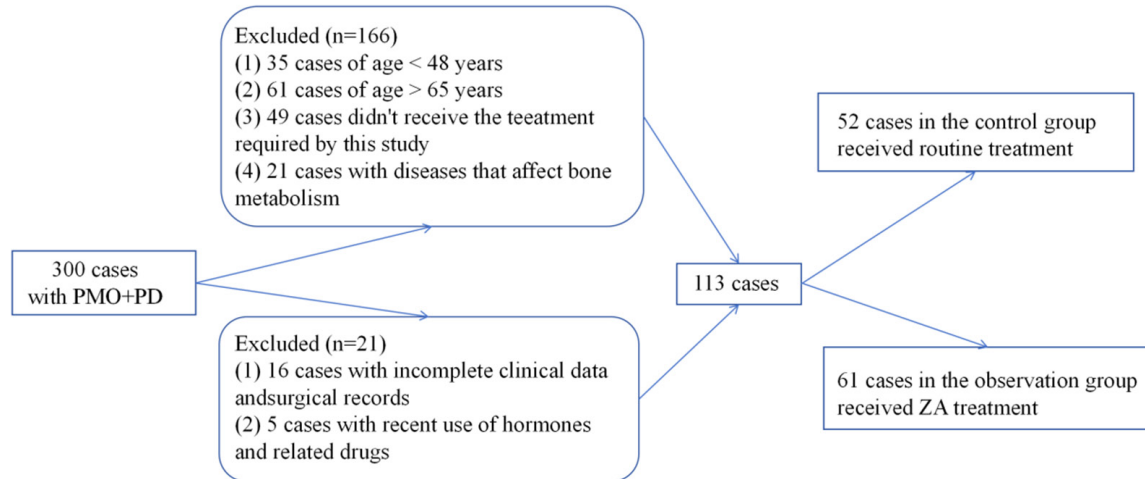


Figure 1. Flowchart of patient selection.

to prevent hip, vertebral, and non-vertebral fractures [8]. Its anti-resorptive action in OP likely involves inhibition of the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT) pathway [9]. Additionally, ZA has been shown to induce osteoclast apoptosis in ovariectomized rats by activating the nuclear factor kappa-B (NF- κ B) pathway, which suppresses osteoclast formation and promotes bone homeostasis [10]. ZA has also demonstrated benefits in increasing bone mineral density (BMD) across different age groups, partially preventing bone loss [11]. Its potential in treating PD has also been reported: Raj et al. [12] found that a 0.05% ZA gel, applied locally, significantly improved periodontal indices in patients with stage III, grade B PD. In another study, Leite de Marcelos et al. [13] observed that ZA intervention in experimental PD models reduced alveolar bone resorption and inhibited disease progression.

Current clinical research on using ZA for PMO+PD remains limited, and this study aims to contribute to this field by providing further analysis and clinical perspectives.

Materials and methods

Patient selection

This study included 113 PMO+PD patients admitted from May 2021 to February 2024. Of these, 52 patients in the control group received routine treatment, while 61 patients in the

observation group received ZA treatment. The study received approval from the Ethics Committee of the General Hospital of Shenzhen University, and relevant medical records were accessed via the hospital's electronic medical record system. Inclusion and exclusion criteria are detailed below, and patient selection is illustrated in **Figure 1**.

Inclusion Criteria: Diagnosis of PMO complicated by PD; no recent use of hormones or related medications; no history of limb immobilization or prolonged bed rest; no systemic abnormalities or diseases affecting bone metabolism; normal communication and cognitive abilities; and willingness to cooperate with the study.

Exclusion Criteria: Age <48 or >65; presence of uterine fibroids, endometriosis, endometrial cancer, or hematologic diseases; long-term use of steroids, anticonvulsants, or anticoagulants; use of bisphosphonates within the past year, calcium supplements within six months, or fluoride within one month; comorbidities including diabetes, cancer, enteritis, malabsorption, peptic ulcers, renal impairment, or liver injury; urinary calcium excretion >400 mg/day; pregnancy or lactation; and severe mental disorders.

Treatment protocol

All patients received conventional supragingival cleaning, with calculus removal via subgingival ultrasonic scaling. Periodontal pockets were irrigated with normal saline, and tinidazole

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muco-adhesive buccal tablets (0.5 mg each) were inserted into the pockets, with 2-3 tablets per tooth for a 7-day course. The control group received daily calcium carbonate (1500 mg, equivalent to 600 mg calcium) and 3200 IU of vitamin D. The observation group received a single 100 mL:5 mg intravenous infusion of ZA over at least 15 minutes, with 250 mL of physiological saline or 5% glucose administered for hydration before and after infusion. Treatment plans were individualized, allowing patients to choose their preferred method based on a full understanding of benefits and limitations, rather than by random selection.

Data collection

Patient data were extracted from the medical records, including therapeutic efficacy, periodontal indices, serum inflammatory markers, bone metabolism indicators, safety outcomes, and BMD measurements, to compare the clinical efficacy of the two treatment approaches.

Outcome measurement

Therapeutic Effectiveness: Patients were evaluated for treatment efficacy 3 months post-intervention. Marked effectiveness was defined as normalization of periodontal inflammatory markers and indices, with resolution of related symptoms. Effectiveness was defined as improvement in periodontal inflammatory markers and indices, with gradual symptom alleviation. Ineffectiveness referred to cases where periodontal inflammatory markers and indices failed to normalize, with no improvement or worsening of symptoms. The total effective rate was calculated as the percentage of cases showing either effectiveness or marked effectiveness.

Periodontal Indices: Periodontal indices, including attachment loss (AL), probing depth (PD), and gingival bleeding index (GBI), were assessed before and three months after initial periodontal treatment.

Serum Inflammation: Venous blood samples were collected before and three months post-treatment to measure levels of inflammatory markers, such as interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , and C-reactive protein

(CRP), using enzyme-linked immunosorbent assay.

Bone Metabolism: Bone metabolism markers - including N-terminal midfragment of osteocalcin (N-MID), beta-CrossLaps (β -CTx), and human calcitonin (hCT) - were analyzed pre-treatment and three months post-treatment. N-MID and β -CTx were measured using electrochemiluminescence immunoassay, while hCT was quantified by radioimmunoassay.

Safety: Adverse events, such as fever, constipation, and muscle soreness, were recorded throughout the treatment period, and incidence rates were calculated.

BMD: BMD of the lumbar spine (L1-L4) and proximal femur was measured using a bone densitometer before and three months post-intervention.

The primary outcome measures included therapeutic effectiveness, periodontal indices, serum inflammation, bone metabolism, and safety, while the secondary measure was BMD. These metrics aimed to determine the clinical efficacy and advantages of ZA in treating PMO+PD.

Statistical analysis

Quantitative and categorical data were imported into SPSS 22.0 for analysis. Quantitative data were presented as mean \pm SEM, with between-group comparisons conducted using t-tests and within-group comparisons using paired t-tests. Categorical data were expressed as ratios (percentages), and inter-group comparisons of categorical data were analyzed using χ^2 tests. Factors influencing treatment efficacy were identified using a multivariable binary logistic regression model. Statistical significance was set at $P < 0.05$. The sample size for this study was calculated to meet minimum requirements, with a threshold of 42 cases.

Results

Comparison of general information

The two groups showed no statistically significant differences in mean age, disease duration, body mass index (BMI), drinking/smoking history, or marital status (all $P > 0.05$) (**Table 1**).

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Table 1. Comparison of general information [n (%), mean \pm SD]

Variables	n	Control group (n=52)	Observation group (n=61)	χ^2/t	P
Mean age (years)	113	55.42 \pm 4.23	56.11 \pm 4.29	0.858	0.393
Disease course (months)	113	15.62 \pm 5.87	15.11 \pm 7.32	0.404	0.687
Body mass index (kg/m ²)	113	21.67 \pm 2.37	22.30 \pm 2.70	1.307	0.194
History of drinking				0.013	0.909
No	81	37 (71.15)	44 (72.13)		
Yes	32	15 (28.85)	17 (27.87)		
History of smoking				2.251	0.134
No	79	40 (76.92)	39 (63.93)		
Yes	34	12 (23.08)	22 (36.07)		
Marital status				0.776	0.378
Single	26	10 (19.23)	16 (26.23)		
Married	87	42 (80.77)	45 (73.77)		

Table 2. Comparison of effect of zoledronic acid on therapeutic effectiveness

Variables	Control group (n=52)	Observation group (n=61)	χ^2	P
Marked effectiveness	20 (38.46)	36 (59.02)		
Effectiveness	14 (26.92)	18 (29.51)		
Ineffectiveness	18 (34.62)	7 (11.48)		
Total effectiveness	34 (65.38)	54 (88.52)	8.724	0.003

Comparison of therapeutic effectiveness of ZA treatment

In the control group, there were 20 cases with marked effectiveness, 14 cases with effectiveness, and 18 cases deemed ineffective. In contrast, the observation group had 36 cases with marked effectiveness, 18 with effectiveness, and 7 cases of ineffectiveness. The observation group had a significantly higher overall treatment effectiveness rate compared to the control group ($P < 0.05$, **Table 2**). Multivariate analysis further identified the treatment method as a significant factor affecting patient efficacy ($P = 0.003$) (**Table 3**).

Comparison of effect of ZA on periodontal indices

Periodontal indices - AL, PD, and GBI, were evaluated (**Figure 2**). Before intervention, AL values were (5.02 \pm 1.17) mm in the control group and (5.01 \pm 1.27) mm in the observation group, which decreased post-intervention to (3.38 \pm 1.34) mm and (2.50 \pm 0.83) mm, respectively. The PD values in the control group were (5.30 \pm 1.6) mm pre-intervention and

(3.20 \pm 0.98) mm post-intervention, while the observation showed a reduction from (5.26 \pm 1.46) mm to (2.57 \pm 0.59) mm. GBI values decreased from (3.46 \pm 0.80) to (1.71 \pm 0.56) in the control group and from (3.61 \pm 1.12) to (0.75 \pm 0.33) in the observation group. No significant differences were observed between the groups before intervention (all $P > 0.05$). However, all indices improved significantly post-intervention in both groups, with the observation group showing even greater reductions (all $P < 0.05$).

Comparison of effect of ZA on serum inflammatory markers

Serum levels of IL-1 β , TNF- α , and CRP were measured to assess inflammation. Pre-intervention IL-1 β levels were (9.18 \pm 1.87) ng/L in the control group and (9.37 \pm 1.97) ng/L in the observation group, reducing to (7.45 \pm 2.06) ng/L and (4.83 \pm 1.64) ng/L post-intervention, respectively. TNF- α levels in the control and observation groups were (52.38 \pm 5.85) pg/mL and (50.25 \pm 7.62) pg/mL pre-intervention, decreasing to (42.02 \pm 7.48) pg/mL and (25.13 \pm 3.71) pg/mL post-intervention, respectively. CRP levels also decreased from (5.82 \pm 0.91) mg/L to (4.29 \pm 1.27) mg/L in the control group and from (5.99 \pm 1.57) mg/L to (3.01 \pm 0.79) mg/L in the observation group. No significant inter-group differences were noted before intervention (all $P > 0.05$). Post-intervention, all inflammatory markers showed significant reductions in both groups,

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Table 3. Multivariate analysis of factors influencing patient efficacy

Factors	β	S.E.	Wald	P	OR	95% CI
Age (years)	0.504	0.515	0.956	0.328	1.655	0.603-4.544
Disease course (months)	0.027	0.501	0.003	0.958	1.027	0.385-2.740
Body mass index (kg/m ²)	0.422	0.517	0.666	0.414	1.525	0.554-4.198
History of drinking	0.396	0.525	0.569	0.450	1.486	0.531-4.162
History of smoking	-0.090	0.562	0.025	0.873	0.914	0.304-2.753
Marital status	0.730	0.571	1.632	0.201	2.074	0.677-6.354
Therapeutic method	1.561	0.525	8.846	0.003	4.765	1.703-13.333

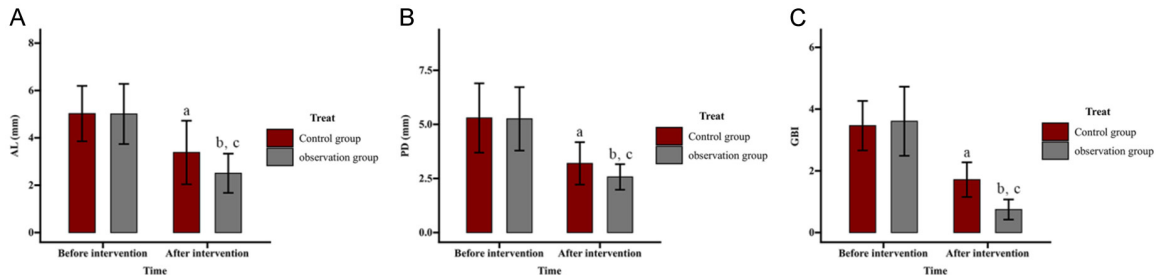


Figure 2. Comparison of effect of zoledronic acid (ZA) on periodontal indices. A. Impact of ZA on AL in patients. B. Impact of ZA treatment on PD in patients. C. Impact of ZA treatment on GBI in patients. Note: ^aP<0.05 and ^bP<0.01 vs. before intervention; ^cP<0.05 vs. Control. AL, attachment loss; PD, probing depth; GBI, gingival bleeding index.

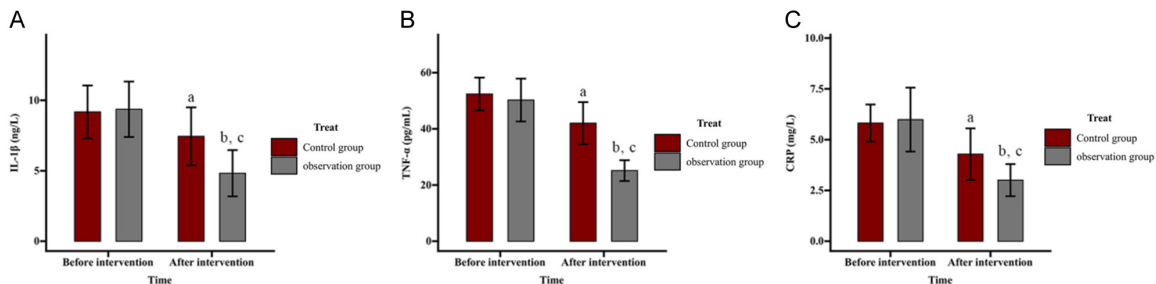


Figure 3. Comparison of effect of zoledronic acid (ZA) on serum inflammation. A. Influence of ZA on IL-1 β in patients. B. Influence of ZA on TNF- α in patients. C. Influence of ZA on CRP. Note: ^aP<0.05 and ^bP<0.01 vs. before intervention; ^cP<0.05 vs. Control. IL, Interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein.

with the observation group demonstrating lower levels than the control group (all P<0.05) (Figure 3).

Comparison of effect of ZA on bone metabolism

Bone metabolism markers, including N-MID, β -CTX, and hCT, were measured, and the results are shown in Figure 4. Pre-intervention, N-MID levels were (14.33 \pm 2.78) ng/mL in the control group and (14.64 \pm 3.06) ng/mL in the observation group, decreasing post-intervention to (11.88 \pm 2.48) ng/mL and (9.23 \pm 1.42) ng/mL, respectively. β -CTX levels were (0.40 \pm 0.06) ng/mL and (0.38 \pm 0.10) ng/mL pre-

intervention and dropped to (0.31 \pm 0.07) ng/mL and (0.21 \pm 0.05) ng/mL post-intervention in the control and observation groups, respectively. For hCT, levels decreased from (2.68 \pm 0.59) ng/L to (2.14 \pm 0.25) ng/L in the control group and from (2.62 \pm 0.47) ng/L to (2.09 \pm 0.33) ng/L in the observation group. No significant differences were observed between groups before intervention (all P>0.05). After intervention, N-MID, β -CTX, and hCT levels decreased significantly in both groups (all P<0.05), with greater reductions in N-MID and β -CTX in the observation group (both P<0.05), while hCT levels showed no significant inter-group difference (P>0.05).

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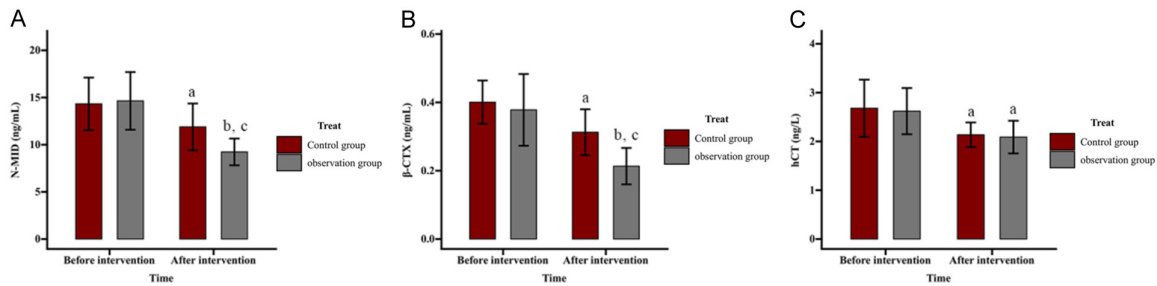


Figure 4. Comparison of effect of zoledronic acid (ZA) on bone metabolism. A. Influence of ZA on N-MID in patients. B. Influence of ZA on β -CTX in patients. C. Influence of ZA on hCT in patients. Note: ^aP<0.05 and ^bP<0.01 vs. before intervention; ^cP<0.05 vs. Control. N-MID, N-terminal midfragment of osteocalcin; β -CTX, beta-CrossLaps; hCT, human calcitonin.

Table 4. Comparison of effect of zoledronic acid treatment on patient complications

Safety	Control group (n=52)	Observation group (n=61)	χ^2	P
Fever	0 (0.00)	6 (9.84)		
Constipation	4 (7.69)	0 (0.00)		
Muscular soreness	0 (0.00)	2 (3.28)		
Total	4 (7.69)	8 (13.11)	0.870	0.351

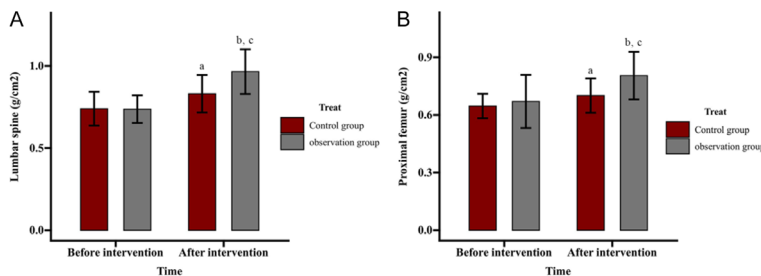


Figure 5. Comparison of effect of zoledronic acid (ZA) on bone mineral density. A. Effect of ZA on bone mineral density of the lumbar vertebrae in patients. B. Effect of ZA on bone mineral density of the proximal femur in patients. Note: ^aP<0.05 and ^bP<0.01 vs. before intervention; ^cP<0.05 vs. Control.

Comparison of effect of ZA treatment on patient complications

The incidence of adverse events, including fever, constipation, and muscle soreness, was similar between the groups, with no significant difference in the overall rate of adverse reactions (7.69% vs. 13.11%, P>0.05) (Table 4).

Comparison of effect of ZA on BMD

BMD of the lumbar spine and proximal femur was assessed. Pre-intervention BMD of lumbar vertebrae L1-L4 was (0.74 ± 0.10) g/cm² in the

control group and (0.74 ± 0.08) g/cm² in the observation group, which increased post-intervention to (0.83 ± 0.11) g/cm² and (0.96 ± 0.14) g/cm², respectively. The proximal femur BMD rose from (0.65 ± 0.06) g/cm² to (0.70 ± 0.09) g/cm² in the control group and from (0.67 ± 0.14) g/cm² to (0.80 ± 0.12) g/cm² in the observation group. No significant inter-group differences were found in lumbar and femur BMD pre-intervention (both P>0.05). Post-intervention, BMD increased significantly in both groups, with more pronounced improvements in the observation group (both P<0.05) (Figure 5).

Discussion

PD is a chronic inflammatory condition affecting the supporting structures of the teeth, and its systemic effects may increase the risk of OP [14]. While the pathogenesis of PD involves dysbiotic biofilms, the progression of inflammation and disruption of bone homeostasis can predispose individuals to OP [15, 16]. This study primarily evaluates the effects of ZA on periodontal indices, serum inflammation, and bone metabolism in patients with PMO complicated by PD, as detailed below.

In this study, the observation group showed a significantly higher total treatment effective

rate than the control group (88.52% vs. 65.38%), indicating that ZA treatment in PMO patients with PD enhances therapeutic effectiveness. A meta-analysis of randomized controlled trials supports the efficacy of ZA in improving BMD in the lumbar spine, femoral neck, and trochanter in PMO patients, while reducing fracture risk with a favorable safety profile [17]. Additionally, a randomized clinical trial by Taguchi et al. [18] indicated that ZA use in PMO patients may help prevent symptomatic periodontal disease. The efficacy of ZA in treating PMO+PD appears partly due to its inhibition of osteoclast differentiation and induction of osteoclast apoptosis, which reduce bone resorption, increase BMD, and positively affect alveolar bone preservation [13, 19].

This study further identified the treatment method as a significant independent factor influencing patient efficacy, underscoring the clinical effectiveness and reliability of ZA treatment. Additionally, improvements in periodontal indices - AL, PD, and GBI were observed in both the groups, with significantly lower AL, PD, and GBI levels in the observation group compared to the control group. This suggests that ZA treatment provides superior improvement in periodontal health for PMO+PD patients. Previous research indicates that ZA's protective effects on periodontal tissues may be related to its inhibition of transforming growth factor β -induced fibrosis in human gingival fibroblasts [20]. Supporting this, Raj et al. [12] reported that ZA significantly reduced PD indices in patients with stage III, grade B periodontitis, consistent with our findings.

The observation group exhibited notably lower levels of inflammatory markers (IL-1 β , TNF- α , and CRP) post-intervention compared to both pre-intervention levels and the control group, indicating that ZA treatment for PMO+PD patients effectively reduces serum hyperinflammation. These markers, including IL-1 β , TNF- α , and CRP, are known to contribute to systemic bone loss and remodeling through inflammatory mediators [21, 22]. Consistent with our findings, ZA significantly inhibited pro-inflammatory cytokines like IL-1 β and TNF- α and reduced bone resorption in a mouse model of apical PD [23].

Post-intervention, the observation group also showed marked improvements in bone metabo-

lism indices (N-MID, β -CTX, and hCT), with significantly greater improvements than the control group (except for hCT), indicating ZA's positive effect on bone metabolism in PMO patients with PD. A meta-analysis by Zhuang et al. [24] supports our findings, demonstrating that ZA improved bone metabolism indices such as N-MID and β -CTX and increased BMD in patients with osteoporotic vertebral compression fractures. Huang et al. [25] also found that ZA, compared to pamidronic acid in treating bone metastases from non-small cell lung cancer, significantly reduced N-MID levels and lowered serum inflammatory markers like TNF- α and CRP, aligning with our observations.

In terms of safety, the overall incidence of adverse events, including fever, constipation, and muscle soreness, was similar between the two groups, suggesting that ZA is safe for treating PMO with PD. This aligns with findings from a meta-analysis by Wang et al. [26], which indicated that long-term ZA use in PMO patients has fewer gastrointestinal adverse events than alendronate, further supporting our results. Additionally, the observation group demonstrated a clear advantage in increasing BMD of the lumbar spine and proximal femur compared to the control group. Yoshizawa et al. [27] similarly reported that ZA improved BMD in OP patients undergoing distal radius fracture surgery. Furthermore, Huang et al. [28] highlighted that ZA improves appendicular skeletal muscle mass and index, benefiting muscle levels in OP patients. ZA has also been shown to be more cost-effective than alendronate for PMO treatment, regardless of age [29].

In summary, ZA treatment for PMO patients with PD enhances therapeutic effectiveness, improves periodontal indices, reduces serum inflammation, supports bone metabolism, and increases BMD, while maintaining a favorable safety profile, making it a valuable option for clinical application. Our findings offer an effective treatment choice for PMO patients with PD and provide new clinical insights for managing this patient population.

Acknowledgements

This study was supported by Guangdong scientific research foundation (No. A2022435); and Science, Technology and Innovation Commotion of Shenzhen Municipality, General

project of Shenzhen University Stability Support Program (No. 20220810161720001).

Disclosure of conflict of interest

None.

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