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Clinical outcomes and safety of combined calcitriol and bisphosphonates in treating postmenopausal osteoporosis: a retrospective cohort study

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Abstract

Objective Despite the well-known benefits of calcitriol and bisphosphonates in managing osteoporosis, limited research has explored the combined therapeutic effects of these agents on bone metabolism, immune function, and clinical outcomes in postmenopausal osteoporosis patients. This study aims to evaluate the clinical efficacy and safety of calcitriol combined with bisphosphonates in the treatment of postmenopausal osteoporosis through a retrospective cohort analysis.

Methods A total of 152 postmenopausal osteoporosis patients treated at our hospital from March 2019 to June 2021 were enrolled and divided into two groups based on the treatment received. The control group received calcitriol alone, while the study group received calcitriol combined with bisphosphonates. Treatment outcomes were assessed by comparing Visual Analogue Scale (VAS) scores for pain, Barthel Index for daily living ability, and Oswestry Disability Index (ODI) for dysfunction before and after treatment. Bone metabolism markers (BALP, BGP, PINP, TRACP), immune cytokines (IL-6, TGF-β1, TNF-α, IL-10), and bone mineral density (BMD) were measured. The incidence of adverse reactions was also recorded.

Results The total effective rate in the study group was 96.05%, significantly higher than 84.21% in the control group ($P < 0.05$). Post-treatment VAS and ODI scores decreased significantly in both groups, with greater improvement in the study group ($P < 0.05$). Barthel Index scores increased more in the study group ($P < 0.05$). Bone metabolism markers (BALP, BGP, PINP, TRACP) and inflammatory cytokines (IL-6, TGF-β1, TNF-α) decreased more significantly in the study group, while IL-10 levels and BMD increased more markedly ($P < 0.05$). The incidence of adverse reactions was lower in the study group (2.63%) than in the control group (5.26%), but the difference was not statistically significant ($P > 0.05$).

Conclusion The combination of calcitriol and bisphosphonates demonstrates superior clinical efficacy and safety in treating postmenopausal osteoporosis, effectively reducing pain and disability, enhancing bone metabolism and immune function, and improving bone mineral density and daily living ability.

Keywords Calcitriol, Bisphosphonates, Postmenopausal OP, Clinical efficacy, Safety evaluation, Retrospective study

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Introduction

Osteoporosis (OP) is assigned into primary and secondary, of which primary is assigned into type I and type II. Type I is postmenopausal OP and type II is senile OP [1]. Increased bone fragility leads to fractures. Hip fracture is one of the main reasons for reducing the quality of life of the elderly, and its main cause is OP [2]. However, due to the lack of obvious symptoms in the early stage of OP, it has a certain concealment, so it cannot attract people's attention. Promoting the prevention and treatment of OP can start with early screening of high-risk groups and early medication for the occurrence and development of OP, which is a key link in the prevention and treatment of OP, which has a high incidence in the elderly, especially in postmenopausal women and it is known as the "silent killer" because of its long incubation period and no obvious symptoms in the early stage [3]. In the advanced stage, joint pain appears as a common symptom in patients, and once this symptom occurs, most patients choose to rest rather than actively diagnose and treat [4]. According to statistics, as of 2019, the number of people with OP in the world has exceeded 200 million, and an average of 20 fractures are caused by OP every minute. The incidence of OP in the elderly is relatively high, and once a hip fracture occurs, it will directly lead to an increase in disability and mortality in the elderly [5]. In 2018, the National OP Foundation (NOF) statistics indicated that 1.5–2 million of the existing 10 million Americans with OP will experience osteoporotic fractures each year [6]. One in eight men over the age of 50 develops an osteoporotic fracture. Thoracic vertebral compression fractures are a common type of osteoporotic fractures and can cause a variety of comorbidities, including back pain, chest tightness, and hunched back, ultimately leading to limited lung function, while lumbar vertebral compression fractures can cause bloating and abdominal pain, constipation and loss of appetite, etc. These diseases predispose older people who are relatively economically disadvantaged to psychological symptoms such as depression and loss of self-esteem [7].

Osteoporotic fractures will bring a heavy burden to society and economy. Clinical data show that patients disabled by OP-related diseases have longer hospital stays than patients with other chronic diseases, which will lead to a dramatic increase in medical costs for OP-related diseases [8]. Osteoporotic fractures primarily affect elderly individuals and postmenopausal women, commonly occurring in the lumbar spine, thoracic spine, and hip, with increased recurrence risk [9]. It is estimated that by 2035 and 2050, there will be 4.83 and 5.99 million patients with osteoporotic fractures in China, and the medical expenses will be as high as 132 and 163 billion RMB. In China, according to the meta-analysis of Meng et al., the overall prevalence of OP among people over 60 years old in my country are 18.5% in women and 14.3% in men [9, 10].

OP has become a common disease in the middle-aged and elderly population. Based on the above studies, the following conclusions can be drawn: In the past five years, the incidence of OP in the middle-aged and elderly in my country has increased significantly, and the related problems of the middle-aged and elderly are more obvious. In addition, age was positively associated with the incidence of OP. The above conclusions are consistent with the Chinese guidelines for the diagnosis and treatment of OP in the elderly (2018). Preventing and delaying the occurrence of OP requires early screening and application of corresponding drugs.

Although both calcitriol and bisphosphonates are established treatments for postmenopausal osteoporosis, limited studies have evaluated their combined effects on bone metabolism, immune function, and clinical outcomes. This study is novel in that it explores the synergistic impact of combining these two agents, providing new insights into improving bone mineral density, reducing pain, and enhancing functional ability in postmenopausal osteoporosis patients. The findings contribute to the growing body of evidence supporting combination therapies in osteoporosis management [9, 11].

Calcitonin plays an important role in the mechanism of human bone metabolism, which is a peptide hormone with 32 amino acid residues. Its main physiological function in the body is to reduce blood calcium concentration, regulate bone metabolism, inhibit bone resorption, and then increase BMD, especially the content of spongy bone [12]. In addition, vitamin D, an important component involved in bone resorption, also plays an indispensable role in maintaining bone mass in the elderly. Human skin produces small amounts of vitamin D when exposed to sunlight. As one of the metabolites of vitamin D, calcitriol has strong biological activity, which can not only promote the absorption of calcium and phosphorus in the intestinal tract, stimulate the synthesis of alkaline phosphatase and osteocalcin by osteoblasts, but also inhibit bone resorption [13]. According to guideline recommendations, in addition to vitamin D and calcium supplementation, bisphosphonates are an important means of treating OP [14]. Bisphosphonates are bone resorption inhibitors and are one of the most commonly used drugs for the treatment of OP. Studies have indicated that zoledronic acid can comprehensively enhance bone mineral density, inhibit bone resorption of osteoclasts, reduce fracture risk and bone pain [15], and promote patients' living standards, but there is a lack of evidence to support relevant laboratory medicine. Based on this, this article discusses 152 postmenopausal OP

patients admitted to our hospital from March 2019 to June 2021 as the research objects.

While calcitriol and bisphosphonates have shown efficacy in treating osteoporosis individually, their combined effects on clinical and biochemical outcomes remain understudied. This study aims to address this gap by evaluating the combined treatment's impact on bone metabolism markers, immune cytokines, and clinical outcomes. Understanding the potential synergistic effects of these agents could lead to improved therapeutic strategies for postmenopausal osteoporosis.

Patients and methods

Normal information

A total of 152 patients with postmenopausal OP who were treated in our hospital from March 2019 to June 2021 were enrolled as the research subjects, their clinical data were collected, and retrospective analysis was conducted, and they were assigned into study groups according to their treatment methods. And the patients who received calcitriol treatment were used as the control group, and the patients treated with calcitriol combined with bisphosphonates were used as the research group. In the control group, the age ranged from 62 to 83 years, with an average of (71.83 ± 4.23) years, and the average menopause time was (14.52 ± 6.64) years; The course of disease ranged from 0.72 to 6 years, with an average course of disease of (4.73 ± 1.42) years; In the study group, the age ranged from 63 to 82 years, with an average age of (72.21 ± 4.46) years, and the average menopause time was (15.31 ± 6.57) years; The course of disease ranged from 0.75 to 6 years, with an average course of disease of (4.56 ± 1.24) years. The general data of patients were not statistically significant. The elevated menopausal age observed in this study, exceeding normative ranges, may correlate with cohort characteristics (e.g., chronic conditions affecting hormonal profiles) or the lack of differentiation between natural and surgical menopause, necessitating further stratification in future investigations. And all patients signed informed consent.Standard constrain: (1) For postmenopausal women, the diagnostic criteria refer to the "Guidelines for Primary Care of Primary Osteoporosis (Practical Edition 2019)" [15] revised by the Chinese Medical Association OP and Bone Mineral Disease Branch: Based on Bone mineral density T value of left femoral neck and left distal 1/3 of radius measured by dual energy X-ray absorptiometry ≤ -2.5; (2) No cognitive, language, intellectual dysfunction, with basic reading and writing skills; (3) Menopause ≥ 5 years; (4) Those who can accept and answer telephone follow-up; (5) Weight-bearing or spontaneous low back pain; (6) Patients Informed consent was obtained and signed the informed consent form.

Exclusion criteria: (1) Patients with severe heart, liver, and renal insufficiency, malignant tumors and other diseases; (2) Those with diabetes, liver, kidney and cardiovascular system diseases; (3) Those who refuse to participate; (4) Those with lupus erythematosus, psoriasis, Patients with autoimmune diseases such as gout, rheumatoid arthritis, and ankylosing spondylitis; (5) Those who use glucocorticoids, long-term drinking, etc. that affect bone metabolism; (6) Those who have irregular follow-up visits.

Treatment methods

Both groups were routinely given calcium carbonate and vitamin D. And calcitriol (Qingdao Zhengdahaier Pharmaceutical Co., Ltd., H20030491) was used for the treatment, 0.25 μg/time, 2 times/d. The research group was treated with calcitriol combined with bisphosphonates alendronate sodium (Merck Sharp & Dohme Italia SPA, Chinese medicine Zhunzi C14202011827), alendronate 70mg/time, once/w, the usage and dosage of calcitriol were the same in the control group, and patients were treated for 9 consecutive months.

Observation indicator

Efficacy evaluation criteria

The clinical efficacy was evaluated according to the patients' joint pain and bone mineral density, and it was assigned into three grades: markedly effective, effective and ineffective. After treatment, the joint pain disappeared and the bone mineral density increased significantly, which was markedly effective; after treatment, the joint pain was relieved and the bone density did not change significantly, which was effective. Failure to meet the above standards, or even aggravated trend is invalid. Total effective rate = apparent rate + effective rate.

VAS score

Visual Analogue Scale/Score (VAS) [16]: 0 points: No pain; < 3 points: Mild pain, tolerable; 4–6 points: Pain and affect sleep; 7–10 points: Intense pain, difficult Endure, affect life.

ODI score

The Oswestry Disability Index (ODI) [17] evaluated and compared the degree of dysfunction before and after treatment, including 10 items such as pain intensity, sleep, and social life. The higher the score, the more serious the dysfunction.

Barthel index

The Barthel index [18] was used to evaluate the daily living ability of patients before and after the intervention, with a total score of 100 points, and the higher the score, the stronger the daily living ability.

Bone metabolism index detection

CobasE602 automatic electrochemiluminescence analyzer (Roche Diagnostics, Switzerland) or Enzyme-linked immunosorbent assay were used to detect the tartrate-resistant acid phosphatase (TRACP), the N-terminal propeptide of type I procollagen (PINP) molecules, the bone alkaline phosphatase (BALP) and osteocalcin (BGP) in patients before treatment and after treatment. Enzyme-linked immunosorbent assay was used to detect the immune cytokines interleukin-6 (IL-6) and interleukin-10 (IL-10), transforming growth factor-β1 (TGF-β1) and tumor necrosis factor-α (TNF-α) levels before treatment and after treatment using the enzyme-linked immunosorbent assay detection kits and related reagents by Ai Meijie Technology Co., Ltd. supply.

Adverse reactions

The incidence of adverse reactions such as dizziness, nausea, fever, chills and other adverse reactions during the medication process were counted.

Statistical analysis

SPSS 19.0 software was adopted for data analysis, among which measurement data including VAS score, Barthel index, ODI score, bone metabolism index, etc. were expressed as ($\overline{x} \pm s$), and independent samples t-test was employed; count data included clinical efficacy, adverse reactions Chi-square test was adopted for the incidence. $P < 0.05$ was considered statistically significant.

Results

Comparison of treatment effects between the two groups

First of all, we compared the therapeutic effects. In the research group, 45 cases were markedly effective, 28 cases were effective, and 3 cases were ineffective, with an effective rate of 96.05%; in the control group, 28 cases were markedly effective, 36 cases were effective, and 12 were ineffective. The efficiency is 84.21%; Compared between groups, the total effective rate of treatment in the study group was higher compared to the control group ($P < 0.05$). All results are indicated in Fig. 1.

VAS rating comparison

We compared the VAS scores. Before treatment, there exhibited no significant difference ($P > 0.05$); After treatment, the VAS scores of patients were decreased. Compared between the groups, the VAS scores of the study group were significantly lower compared to the control group at 1 month, 2 months after treatment, and 3 months after treatment ($P < 0.05$). All results are indicated in Table 1.

ODI rating comparison

We compared the ODI scores. Before treatment, there exhibited no significant difference ($P > 0.05$); After treatment, the VAS scores of patients were decreased. Compared between the two groups, the VAS scores of the study group at 1 month, 2 months after treatment and 3 months after treatment were significantly lower

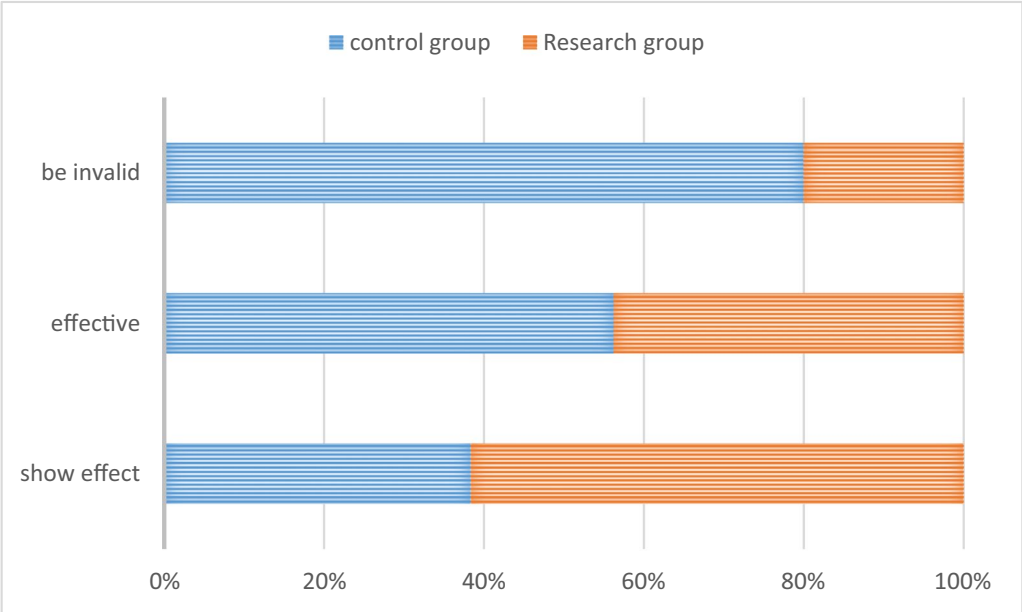

Fig. 1 Comparison of the treatment effects of the two groups of patients

compared to the control group (P < 0.05). All results are indicated in Table 2.

Barthel index score comparison

We *compared* the Barthel index scores. Before treatment, there exhibited no significant difference ($P > 0.05$); After treatment, the Barthel index scores increased. Compared with the two groups, the Barthel index scores of the study group were higher compared to the control group at 1 month, 2 months and 3 months after treatment ($P < 0.05$). All results are indicated in Table 3.

Comparison of bone metabolism index levels

We compared the levels of bone metabolism indexes. Before treatment, there exhibited no significant difference ($P > 0.05$); After treatment, the levels of bone metabolism indexes decreased. Compared between the two groups, the levels of BALP, BGP, PINP and TRACP in the study group were lower compared to the control group ($P < 0.05$). All results are indicated in Table 4.

Comparison of immunocytokine expression levels

We compared the expression levels of immune cytokines. Before treatment, there was no significant difference ($P > 0.05$); After treatment, the levels of IL-6, TGF-β1 and TNF-α were decreased, and the level of IL-10 was increased. Compared with the two groups, the improvement degree of the study group was significantly better compared to the control group ($P < 0.05$). All results are indicated in Table 5.

Bone density contrast

We compared the bone mineral density. Before treatment, there exhibited no significant difference ($P > 0.05$); After treatment, the bone mineral density of the patients increased. Compared with the two groups, the improvement degree of the study group was significantly better compared to the control group ($P < 0.05$). All results are indicated in Table 6.

Comparison of adverse reactions

We compared the occurrence of adverse reactions. One patient in the study group developed dizziness and one

Table 1 Comparison of VAS scores between the two groups of patients[$\overline{x} \pm s$, Points]

Group	N	Before treatment	1 month after treatment	2 months after treatment	3 months after treatment
C group	76	6.13 ± 2.08	4.83 ± 1.76	1.84 ± 0.56	1.02 ± 0.33
R group	76	5.88 ± 2.16	3.67 ± 1.14	0.92 ± 0.59	0.78 ± 0.04
t		0.727	4.823	9.860	6.294
P		> 0.05	< 0.01	< 0.01	< 0.01

Table 2 Comparison of ODI scores of the two groups of patients[$\overline{x} \pm s$, Points]

Group	N	Before treatment	1 month after treatment	2 months after treatment	3 months after treatment
C group	76	73.61 ± 7.34	28.51 ± 2.33	28.33 ± 2.62	28.15 ± 2.66
R group	76	73.55 ± 7.26	26.89 ± 3.45	25.41 ± 3.46	26.47 ± 3.26
t		0.051	3.392	5.865	4.227
P		> 0.05	< 0.01	< 0.01	< 0.01

Table 3 Comparison of Barthel index scores between the two groups of patients[$\overline{x} \pm s$, Points]

Group	N	Before treatment	1 month after treatment	2 months after treatment	3 months after treatment
C group	76	32.45 ± 3.43	47.83 ± 3.49	55.16 ± 5.54	78.13 ± 4.65
R group	76	33.08 ± 3.57	59.66 ± 4.82	67.36 ± 3.59	86.13 ± 5.57
t		1.109	17.331	16.402	9.612
P		> 0.05	< 0.01	< 0.01	< 0.01

Table 4 Comparison of bone metabolism index levels before and after treatment in the two groups of patients[$\overline{x} \pm s$]

Group	N	BALP(IU/L)		BGP(ng/ml)		PINP(ng/ml)		TRACP (μg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
C group	76	74.63 ± 8.14	65.12 ± 6.35[a]	10.67 ± 2.15	6.93 ± 1.05[a]	65.34 ± 7.45	55.72 ± 5.01[a]	4.16 ± 1.03	3.28 ± 0.66[a]
R group	76	74.67 ± 8.12	56.73 ± 5.18[b]	10.56 ± 2.16	4.28 ± 0.65[b]	65.37 ± 7.68	35.18 ± 3.06[b]	4.18 ± 1.01	2.04 ± 0.25[b]
t		0.030	8.925	0.315	18.708	0.024	30.502	0.121	15.317
P		> 0.05	< 0.01	> 0.05	< 0.01	> 0.05	< 0.01	> 0.05	< 0.01

Comparison before and after treatment in the control group, [a]$P < 0.05$; Comparison of research group before and after treatment, [b]$P < 0.05$

Table 5 Comparison of the expression levels of immune cytokines in the two groups of patients before and after treatment[$\overline{x} \pm s$]

Group	N	IL-6(ng/L)		IL-10(ng/L)		TGF-β_1(ng/L)		TNF-α (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
C group	76	125.26 ± 12.38	110.22 ± 11.65[a]	29.37 ± 3.51	36.48 ± 3.87[a]	5.28 ± 1.08	6.34 ± 1.32[a]	5.88 ± 1.04	4.55 ± 0.93[a]
R group	76	125.34 ± 12.32	84.21 ± 8.17[b]	29.45 ± 3.17	46.35 ± 5.66[b]	5.26 ± 1.01	8.08 ± 2.25[b]	5.83 ± 1.05	3.18 ± 0.56[b]
t		0.040	15.935	0.147	12.549	0.118	5.815	0.295	11.002
P		> 0.05	< 0.01	> 0.05	< 0.01	> 0.05	< 0.01	> 0.05	< 0.01

Comparison before and after treatment in the control group, [a]$P < 0.05$; Comparison of research group before and after treatment, [b]$P < 0.05$

Table 6 Comparison of bone mineral density in two groups of patients before and after treatment[$\overline{x} \pm s$]

Group	N	Femoral neck(g/cm^2)		Lumbar spine(g/cm^2)		Ward triangle(g/cm^2)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
C group	76	0.61 ± 0.23	0.77 ± 0.16	0.65 ± 0.17	0.71 ± 0.11	0.72 ± 0.13	0.77 ± 0.12
R group	76	0.64 ± 0.21	0.92 ± 0.14	0.68 ± 0.14	0.92 ± 0.17	0.68 ± 0.18	0.89 ± 0.13
t		0.840	6.151	1.187	9.041	1.571	5.913
P		> 0.05	< 0.01	> 0.05	< 0.01	> 0.05	< 0.01

patient developed chills, with an adverse reaction rate of 2.63%. In the control group, two patients had fever and two patients developed chills, with an adverse reaction rate of 5.26%; Compared between groups, the total incidence of adverse reactions in *the* study group was lower compared to the control group, and the difference exhibited not statistically significant ($P > 0.05$). All results are indicated in Fig. 2.

Discussion

With the deepening of the aging of my country's population, the number of elderly people has increased rapidly. According to the survey, at present, about 138 million people in my country are aged 65 and above, accounting for 10.1% of all residents [19]. Officials predict that by 2050, the degree of aging in my country will further intensify, and the ratio will reach 33.3%. At present, the incidence of fractures is higher in elderly diseases, among which osteoporosis (OP) accounts for 6.6% of fractures, and 36% of people over 60 years old are osteoporotic patients, so OP is a great threat to the health of the elderly. By 2050, the elderly population, especially women, will suffer from OP and osteoporotic fractures will further increase, seriously affecting the quality of life of the elderly. Analyzing the risk factors of OP and giving effective drug treatment is an effective way to effectively reduce the incidence of fractures caused by OP However, due to the high price of anti-OP drugs and many adverse reactions, the clinical prevention and treatment of OP is not optimistic. Therefore, it is necessary to study the prevention and treatment strategies of OP with low cost and in line with my country's national conditions.

Calcium supplementation is the drug basis for the prevention and treatment of OP. Ingestion of calcium tablets in the form of supplements rapidly increased circulating calcium concentrations, decreased parathyroid hormone levels and markers of bone resorption, and decreased markers of bone formation after 2–3 months [19]. In the first year of treatment, bone density in the hip and spine increased by 0.5–1%. In most trials, no relationship was

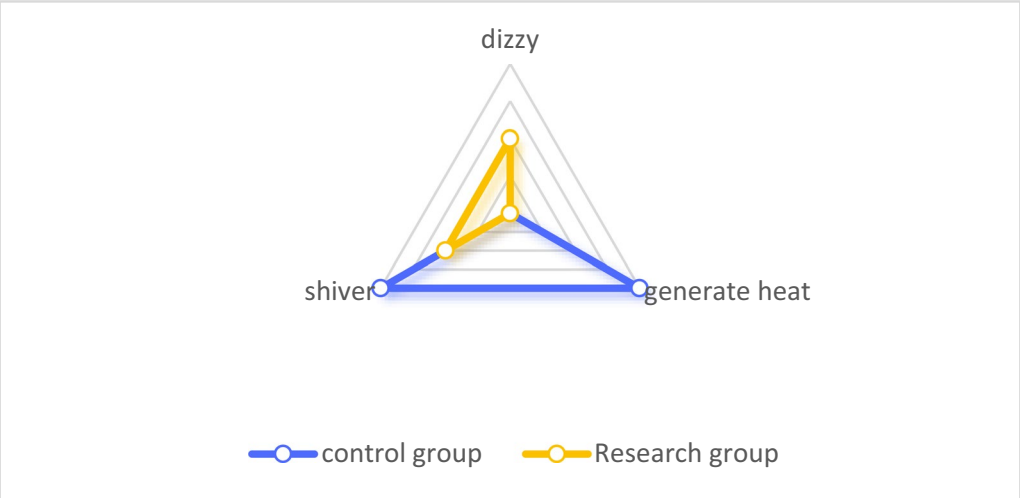

Fig. 2 Comparison of adverse reactions between the two groups

found between an individual's baseline dietary calcium intake and bone mineral density response. In general, calcium doses ≥ 1000 mg/day were used in supplement studies. Studies have found that, with the exception of people with very low calcium intake, doses of 250–600 mg per day have little or no effect on bone mineral density [20]. Collectively, these findings suggest that calcium supplementation, as a less potent antiresorptive agent, reduces bone turnover regardless of baseline calcium intake. However, in terms of bone mass, this did not yield much benefit. In a full analysis, there was a 43% reduction in hip fractures, which equated to a 26% reduction in fracture rates on an intention-to-treat basis. The effect at 36 months was similar. At 18 and 36 months, the number of nonvertebral fractures decreased by 25% and 17%, respectively. Conclusions suggest that calcium and vitamin D are important components of OP treatment because of their anti-fracture efficacy and high safety profile.

The study by CanoA and his colleagues included more frail older women, and 12 months after the start of the study, the calcium intake of the placebo subjects was 500 mg/day, and the mean serum 25-hydroxyvitamin D concentration was 25 nmol/L, which is equivalent to 13.7 nmol/L after correcting the measurement error [21].

In the past 10 years, the results of some larger trials of calcium supplementation have been reported. In the primary analysis, no beneficial effect on fracture was found, but in the secondary analysis, there were also some findings of beneficial and negative effect. This was found in a recent meta-analysis, where numerous studies have indicated that calcium has little or no effect on fractures [22]. Among the community-dwelling subjects, the total number of fractures was reduced by only 6%. However, this may be related to a reduction in the duration of trials for fracture prevention and a decrease in the compliance of enrolled patients. There was no use hip fracture as a separate endpoint, but at least three meta-analyses indicated an upward trend in the use of calcium alone for hip fracture [23]. The effect of calcium plus vitamin D on hip fracture was largely determined by the above findings, but an analysis of community subjects indicated no evidence of fracture prevention. Recently, researchers at the Women's Health Institute (WHI) demonstrated in their study a significant interaction of calcium plus vitamin D and hormone therapy on hip fracture risk. Results in a Meta-analysis of WHI subjects using nonhormonal therapy indicated a trend for an adverse effect of calcium plus vitamin D on hip fracture risk. In conclusion, the benefit of calcium supplementation on bone density was apparently small, but its long-term benefit on bone density was not demonstrated in most studies. Therefore, the anti-fracture efficacy of calcium supplements remains an open question. There is no evidence to support its preventive effect on hip fractures (except in some patients with severe vitamin D deficiency, which has led the U.S. Preventive Services Task Force to not recommend calcium for fracture prevention, and some academic journals support this view [24].

A recent meta-analysis of calcium supplementation studies in older England women from serval prospective calcium use studies raised concerns that calcium supplementation may increase the risk of myocardial infarction [25]. A further meta-analysis included trial data of 28,072 participants from nine studies using calcium

supplementation alone or both calcium and vitamin D. This meta-analysis concluded that calcium supplementation alone, or both calcium and vitamin D, was associated with a 24% increased risk of myocardial infarction and a 15% increased risk of myocardial infarction or stroke. However, upon careful review of these three reports, we can see that these conclusions relied on studies comparing multiple endpoints in heterogeneous populations, and most of the time using suboptimal methods to identify vascular disease. A recent report indicated that in serval randomized controlled trials of calcium administration, subjects receiving calcium had higher rates of self-reported gastrointestinal adverse events, while subjects receiving calcium had self-reported myocardial infarction higher error rate. The authors suggest that the higher error rate in the self-report of myocardial infarction in the calcium group may be due to an increase in functional gastrointestinal disturbances caused by calcium supplementation that was mistaken for myocardial infarction [26]. Notably, in the WHI, the addition of calcium and vitamin D did not increase the risk of cardiovascular disease among participants randomized to take individual calcium supplements.

Conversely, in a study using a more accurate method of vascular disease determination, calcium use and risk of atherosclerotic vascular disease were not found. In this trial, 1460 women with a mean age of (75.1 ± 2.7) years participated in a 5-year randomized, double-blind, placebo-controlled trial of calcium carbonate (1200 mg/day oral calcium or placebo). Complete atherosclerotic vascular hospitalization and mortality data obtained using the Western Australian Datalink System Hospitalization and Mortality Records indicated that calcium was not associated with a higher risk of death [27]. Based on the above results, calcium supplementation alone may reduce bone loss and increase bone density in older men and women. However, most opinion is that the effect of reducing osteoporotic fractures needs to be further confirmed [28]. Regarding the safety of calcium supplementation, a large number of studies have confirmed that calcium supplementation does not increase the incidence of kidney stones. Whether calcium supplementation increases the risk of cardiovascular and cerebrovascular disease has been controversial in recent years, and further clinical research is needed [29–31].

There are a variety of clinical calcium preparations in the domestic market, mainly assigned into inorganic calcium, organic calcium and some traditional Chinese medicine preparations [32–34]. 1) Inorganic calcium: mainly calcium chloride, calcium carbonate, active calcium (the main components are calcium oxide and calcium hydroxide, mainly made of oyster shells and scallop shells after high temperature calcination and hydrolysis) calcium hydrogen phosphate, etc.; 2) natural sources of calcium: such as oyster shells, scallop shells, bone paste, pearls, egg shells, etc.; 3) organic calcium: such as calcium lactate, calcium gluconate, calcium citrate, calcium malate, calcium acetate, calcium glycerophosphate, Calcium glucuronate, calcium aspartate, and calcium L-threonate, but these calcium supplements contain varying amounts of elemental calcium [35]. Since the theoretical content of calcium carbonate is 40%, that is to say, each gram of calcium carbonate contains 400 mg of elemental calcium, calcium carbonate with low water solubility will be absorbed by the human body under the action of gastric acid to form calcium ions. Its advantages are higher calcium content, lower side effects, low price and absorption comparable to milk and other dairy products, so it is widely adopted clinically as a calcium supplement.

Osteotriol is another essential drug for OP prevention and treatment. Overall, calcitriol binds to vitamin D receptors in the kidney, parathyroid gland, gut, and bone, and increases serum calcium levels by promoting intestinal absorption, renal tubular reabsorption, and calcium release from bone [36]. Calcitriol, as a transcription factor, encodes a calcium-binding protein that simultaneously transports calcium and phosphate ions in intestinal epithelial cells. Like parathyroid hormone, calcitriol stimulates bone resorption by activating osteoclasts by releasing nuclear factor receptor activator kappa-B ligand (RANKL) from osteoblasts. A few studies have found that calcitriol significantly inhibits the proliferation of normal human epidermal keratinocytes and T lymphocytes by inducing apoptosis, and inhibits the gene expression of psoriasis-related chemokines and epidermal proteins. In addition, osteotriol can be rapidly absorbed and reach the peak plasma concentration within 3 to 6 h, so the onset of action is quicker. Zoledronic acid belongs to the bisphosphonate class of drugs, which are mostly used for the treatment of hypercalcemia and OP. It can effectively reduce the incidence of fractures, bone diseases and bone pain, and meanwhile relieve symptoms, help prevent osteitis deformans, and is of great value for disease prognosis. Clinical research data show that bisphosphonates have the effects of rapid absorption, strong affinity, less adverse reactions, and relatively long retention time in bone for the body's bones, thereby promoting the increase of bone density. These drugs mainly act on bone osteoclasts, can effectively inhibit the activation of osteoclasts, have an important impact on the activation and final formation of osteoclasts, and can promote the apoptosis of osteoclasts [37]. The treatment of hypercalcemia diseases, OP diseases and tumor bone metastases caused by inflammation is relatively safe, and the treatment effect is satisfactory [38–40]. More

than 200 patients with this disease were assigned into two groups [41]. The control group received conventional treatment, while the experimental group received calcitriol combined with alendronate. The results indicated that the clinical efficacy of the experimental group was significantly better compared to the control group ($P < 0.05$), and the clinical indicators and adverse reactions of the group were significantly better compared to the control group ($P < 0.05$). It is fully suggested that the treatment effect of calcitriol combined with bisphosphonates for OP disease is more obvious compared to other drugs, which can effectively improve symptoms and increase bone density, and the side effects after drug treatment are relatively low.

Bone is a living tissue with metabolic functions. It is a bone turnover process in which osteoblasts are generated and osteoclasts absorb old bone. In this process, biochemical indicators of bone metabolism have important regulatory significance [42, 43]. BALP, BGP, PINP, and TRACP are commonly used clinical indicators for evaluating bone metabolism, and their levels increase after the occurrence of bone diseases. This study indicates that bisphosphonates combined with calcitriol can increase bone mineral density and enhance bone metabolism in patients. Studies have found that the skeletal system is related to the immune system and has many co-regulatory factors, including IL-6, IL-10, TGF-β1, TNF-α, etc., which are related to biological processes such as osteoclast proliferation and differentiation. After OP, the levels of IL-6 and TNF-α decreased, while the levels of IL-10 and TGF-β1 increased. This study found that bisphosphonates combined with calcitriol can enhance the abnormal expression of immune cytokines and promote the abnormality of the skeletal system. In summary, calcitriol combined with bisphosphonates can significantly enhance the immune function of postmenopausal patients with OP, promote abnormal bone metabolism, increase bone mineral density, reduce adverse reactions, and have high safety.

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Author contributions
XZ: Conceptualization, Data curation, Formal analysis, Investiga-tion, Methodology, Resources, Writing – original draft. HL: Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft. J-HW: Conceptualization, Formal analysis, Resources, Supervision, Visualization, Writing – review & editing. ZH: Conceptualization, Formal analysis, Resources, Supervision, Visualization, Writing – review & editing. LC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was reviewed and approved by the Medical Ethic Committee. Informed consent was obtained from all patients who participated in this study.

Consent for publication
All the authors agree to publish the article with responsibility.

Competing interests
The authors declare no competing interests.

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