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Clinical efficacy and outcomes of calcitriol combined with bisphosphonates in the treatment of postmenopausal osteoporosis

A quasi-experimental study

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Abstract

Background: A quasi-experimental study was conducted to investigate the clinical efficacy and outcomes of calcitriol combined with bisphosphonates in the treatment of postmenopausal osteoporosis (OP).

Methods: A total of 152 patients with postmenopausal OP from March 2019 to June 2021 were enrolled. The patients who received calcitriol treatment were adopted as the control group, and the patients treated with calcitriol combined with bisphosphonates were considered as the intervention group. The treatment effects of patients were compared, and the pain degree of the joints of the patients was evaluated by Visual Analogue Scale/Score (VAS), the Barthel Index score was used to evaluate the daily living ability of patients, the hand and Oswestry Disability Index (ODI) were used to evaluate the dysfunction before and after treatment, and the bone metabolism indexes, immune cytokines and bone mineral density were detected before and after treatment, and the incidence of adverse reactions was calculated.

Results: Regarding the therapeutic effects, the intervention group indicated an effective rate of 96.05% while the effective rate was 84.21% in the control group. The total effective rate of treatment in the intervention group was higher than the control group. The VAS, ODI scores, and bone metabolism indexes of the intervention group were significantly lower than the control group at 1, 2, and 3 months after treatment. The Barthel Index scores and bone mineral density of the intervention group were higher than the control group at 1, 2, and 3 months after treatment. The improvement of immune cytokines in the intervention group was significantly better than the control group ($P < .05$). One patient in the intervention group developed dizziness and 1 patient developed chills, with an adverse reaction rate of 2.63%, while in the control group, 2 patients had fever, and 2 patients developed chills, with an adverse reaction rate of 5.26% ($P > .05$).

Conclusion: Calcitriol combined with bisphosphonates has a significant clinical effect in the treatment of postmenopausal OP, which can significantly relieve bone pain in postmenopausal OP patients, enhance abnormal bone metabolism and immune function, and promote bone mineral density and daily living ability.

Abbreviations: BALP = bone alkaline phosphatase, BGP = osteocalcin, BMD = bone mineral density, CT = calcitriol, IL-10 = immune cytokines interleukin-10, IL-6 = immune cytokines interleukin-6, M-CSF = macrophage colony-stimulating factor, ODI = Oswestry Disability Index, OP = osteoporosis, PIPN = peptide, RANKL = receptor activator of nuclear factor kappa-B ligand, TGF-β1 = transforming growth factor-β1, TNF-α = tumor necrosis factor-α, TRACP = tartrate-resistant acid phosphatase, VAS = Visual Analogue Scale/Score.

Keywords: bisphosphonates, calcitriol, clinical efficacy, postmenopausal OP, retrospective study, safety evaluation

1. 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 1 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

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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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]

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.[5] Therefore, preventing and delaying the occurrence of OP requires early screening and application of corresponding drugs.

Calcitriol (CT) plays an important role in the mechanism of human bone metabolism. CT 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 bone mineral density (BMD), especially the content of spongy bone.[6,7] 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 1 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.[8,9] According to guideline recommendations, in addition to vitamin D and calcium supplementation, bisphosphonates are an important means of treating OP.[10] Bisphosphonates are bone resorption inhibitors and are 1 of the most used drugs for the treatment of OP. Studies have indicated that zoledronic acid can comprehensively enhance BMD, inhibit bone resorption of osteoclasts, reduce fracture risk, and bone pain, and promote patients' living standards, but there is a lack of evidence to support relevant laboratory medicine. Therefore, this study aimed to investigate the clinical efficacy and outcomes of calcitriol combined with bisphosphonates in the treatment of postmenopausal osteoporosis (OP).

2. Methods

2.1. Study design, participants, and ethics

This was a quasi-experimental study. A total of 152 patients with postmenopausal OP who were treated in our hospital from March 2019 to June 2021 were enrolled. Participants clinical data were collected, and retrospective analysis was conducted. According to the patient's treatment methods, they were allocated to the control group (patients who received calcitriol treatment) or intervention group (patients treated with calcitriol combined with bisphosphonates).

Inclusion criteria: For postmenopausal women, the diagnostic criteria refer to the "Guidelines for Primary OP Primary Care (Practical Edition 2019)"[10] revised by the Chinese Medical Association OP and Bone Mineral Disease Branch: Based on BMD T value of left femoral neck and left distal 1/3 of radius measured by dual energy X-ray absorptiometry ≤ −2.5; no cognitive, language, intellectual dysfunction, with basic reading and writing skills; menopause ≥ 5 years; those who can accept and answer telephone follow-up; weight-bearing or spontaneous low back pain; patients Informed consent was obtained and signed the informed consent form.

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

This study was permitted by the medical ethics committee of Shanghai Changfeng Community Health Service Center of Putuo District, and all patients signed informed consent.

2.2. Treatment methods

Both groups were routinely given calcium carbonate and vitamin D, and calcitriol (Qingdao Zhenghaier 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 70 mg/time, once/d, the usage, and dosage of calcitriol were the same in the control group, patients were treated for 9 consecutive months.

2.3. Measures

2.3.1. Efficacy evaluation criteria. The clinical efficacy was evaluated according to the patients' joint pain and BMD, and it was assigned into 3 grades: markedly effective, effective, and ineffective. After treatment, the joint pain disappeared and the BMD 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.

2.3.2. VAS score. Visual Analogue Scale/Score (VAS)[11]: 0 points: No pain; <3 points: Mild pain, tolerable; 4 to 6 points: Pain and affect sleep; 7 to 10 points: Intense pain, difficult Endure, affect life.

2.3.3. ODI score. The Oswestry Disability Index (ODI)[12] 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.

2.3.4. Barthel Index. The Barthel Index[13] 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.

2.3.5. Bone metabolism indexes, immune cytokines, and BMD. CobasE602 automatic electrochemiluminescence analyzer (Roche Diagnostics, Switzerland) was used to detect the tartrate-resistant acid phosphatase (TRACP) and the N-terminal front of type I procollagen molecules in patients before treatment and 1 day after treatment. Peptide (PINP) levels. Enzyme-linked immunosorbent assay was used to detect the bone alkaline phosphatase (BALP), osteocalcin (BGP) and immune cytokines interleukin-6 (IL-6) and interleukin before treatment and 1 day after treatment. -10 (IL-10), transforming growth factor-β1 (TGF-β1), tumor necrosis factor-α (TNF-α) levels, enzyme-linked immunosorbent assay detection kits and related reagents by Ai Meijie Technology Co., Ltd. supply.

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

2.4. Statistical analysis

SPSS 19.0 software was used for data analysis, among which measurement data including VAS score, Barthel Index, VAS score, ODI score, bone metabolism index, etc were expressed as mean and standard deviation, and independent samples *t*-test was used for comparison between the 2 groups. Qualitative data including clinical efficacy, adverse reactions were described with frequency and percentage and Chi-square test was used for comparison between the 2 groups. $P < .05$ was considered statistically significant.

3. Results

In the control group (n = 76), 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 intervention group (n = 76), 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 between the 2 groups.

3.1. Treatment effects Comparison

In the intervention 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 intervention group was higher compared to the control group ($P < .05$).

3.2. VAS score comparison

Before treatment, there was no significant difference between the 2 groups, after treatment, the VAS scores of patients decreased. The VAS scores of the intervention group were significantly lower than the control group at 1, 2, and 3 months after treatment ($P < .05$) (Table 1).

3.3. ODI rating comparison

Before treatment, there was no significant difference between the 2 groups, after treatment, the ODI scores of patients were decreased. The ODI scores of the intervention group at 1, 2, and 3 months after treatment were significantly lower than the control group ($P < .05$) (Table 2).

3.4. Barthel Index score comparison

Before treatment, there was no significant difference between the 2 groups, after treatment, the Barthel Index scores increased. The Barthel Index scores of the intervention group were higher than the control group at 1, 2, and 3 months after treatment ($P < .05$) (Table 3).

3.5. Bone metabolism index levels comparison

Before treatment, there was no significant difference between the 2 groups, after treatment, the levels of bone metabolism indexes decreased. The levels of BALP, BGP, PINP and TRACP in the intervention group were lower than the control group ($P < .05$) (Table 4).

3.6. Comparison of immune-cytokine expression levels

Before treatment, there was no significant difference between the 2 groups, after treatment, the levels of IL-6, TGF-β1, and TNF-α were decreased, and the level of IL-10 was increased. The improvement degree of immune-cytokine expression levels in the intervention group was significantly better than the control group ($P < .05$) (Table 5).

3.7. BMD comparison

Before treatment, there was no significant difference between the 2 groups, after treatment, the bone density of the patients increased. The improvement degree of BMD in the intervention group was significantly better than the control group ($P < .05$) (Table 6).

3.8. Comparison of adverse reactions

One patient in the intervention group developed dizziness and 1 patient developed chills, with an adverse reaction rate of 2.63%. In the control group, 2 patients had fever and 2 patients developed chills, with an adverse reaction rate of 5.26%. The total incidence of adverse reactions in the intervention group was lower than the control group but the difference was not statistically significant ($P > .05$).

4. Discussion

Osteoporosis is a metabolic bone disease characterized by decreased bone strength and bone loss, often seen in clinical practice. The condition can be classified into idiopathic and secondary forms based on its cause. Patients with osteoporosis commonly experience symptoms such as back pain and fractures, which not only pose significant health risks but also interfere with daily life and work. Therefore, it is crucial to prioritize the treatment of osteoporosis in clinical settings to enhance bone density, alleviate symptoms, minimize side effects, and improve patients' quality of life.[14,15]

Currently, the primary approach to treating osteoporosis is pharmacological, with various medications available that act through different mechanisms. These drugs can be categorized into basic drugs, bone stimulants, and bone inhibitors, depending on their mode of action.[16] This study found that the combination treatment group, which received both calcitriol and bisphosphonates, achieved a total effective

Table 1

Comparison of pain scores between the 2 groups of patients [$\bar{x} \pm s$, points].

Group	N	Before treatment	1 mo after treatment	2 mo after treatment	3 mo after treatment
Control	76	6.13 ± 2.08	4.83 ± 1.76	1.84 ± 0.56	1.02 ± 0.33
Intervention	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 2 groups of patients [$\bar{x} \pm s$, points].

Group	N	Before treatment	1 mo after treatment	2 mo after treatment	3 mo after treatment
Control	76	73.61 ± 7.34	28.51 ± 2.33	28.33 ± 2.62	28.15 ± 2.66
Intervention	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 2 groups of patients [$\bar{x} \pm s$, points].

Group	N	Before treatment	1 mo after treatment	2 mo after treatment	3 mo after treatment
Control	76	32.45 ± 3.43	47.83 ± 3.49	55.16 ± 5.54	78.13 ± 4.65
Intervention	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 2 groups of patients [$\bar{x} \pm s$].

		BALP (IU/L)		BGP (ng/mL)		PINP (ng/mL)		TRACP (μg/L)	
Group	N	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	76	74.63 ± 8.14	65.12 ± 6.35*	10.67 ± 2.15	6.93 ± 1.05*	65.34 ± 7.45	55.72 ± 5.01*	4.16 ± 1.03	3.28 ± 0.66*
Intervention	76	74.67 ± 8.12	56.73 ± 5.18**	10.56 ± 2.16	4.28 ± 0.65**	65.37 ± 7.68	35.18 ± 3.06**	4.18 ± 1.01	2.04 ± 0.25**
t		0.030	8.925	0.315	18.708	0.024	30.502	0.121	15.317
P		>.05	<.01	>.05	<.01	>.05	<.01	>.05	<.01

*$P < 0.05$; comparison before and after treatment in the control group.

**$P < 0.05$; comparison of research group before and after treatment.

Table 5

Comparison of the expression levels of immune cytokines in the 2 groups of patients before and after treatment [$\bar{x} \pm s$].

		IL-6 (ng/L)		IL-10 (ng/L)		TGF-β_1 (ng/L)		TNF-α (ng/L)	
Group	N	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	76	125.26 ± 12.38	110.22 ± 11.65*	29.37 ± 3.51	36.48 ± 3.87*	5.28 ± 1.08	6.34 ± 1.32*	5.88 ± 1.04	4.55 ± 0.93*
Intervention	76	125.34 ± 12.32	84.21 ± 8.17**	29.45 ± 3.17	46.35 ± 5.66**	5.26 ± 1.01	8.08 ± 2.25**	5.83 ± 1.05	3.18 ± 0.56**
t		0.040	15.935	0.147	12.549	0.118	5.815	0.295	11.002
P		>.05	<.01	>.05	<.01	>.05	<.01	>.05	<.01

*$P < 0.05$; comparison before and after treatment in the control group.

**$P < 0.05$; comparison of research group before and after treatment.

treatment rate of 96.05%, significantly higher than the control group's rate of 84.21%. The main reason is that the superior effectiveness of bisphosphonates in treating osteoporosis lies in their ability to improve disease prognosis. Calcitriol, known for its rapid absorption, strong affinity, minimal side effects, and prolonged retention in bone tissue, also contributes to increased bone density. These medications primarily target fractured bones, effectively preventing osteoclast activation, inhibiting osteoclast formation, and promoting osteoclast apoptosis.[17,18]

Calcitriol is primarily metabolized by the liver and kidneys, and its active metabolite, 1,25-dihydroxyvitamin D3, enhances calcium absorption and regulates calcium (Ca2+) balance.[19] However, the effectiveness of calcitriol when used alone is limited, and it may cause adverse effects such as hypercalcemia and malnutrition.[20] In the present study, the observation group was treated with a combination of calcitriol and bisphosphonates, yielding promising results. Significant outcomes included pain reduction, decreased ODI, increased Barthel Index scores, and lower metabolic index levels. Additionally, improved bone density was a notable finding in this study.

Bisphosphonates, which are structurally similar to pyrophosphates, reduce bone resorption and increase bone mass and density when used in combination with a bone mineralizing matrix. This makes them widely used in clinical practice.[21] Similarly, Rhee et al found that a regimen combining 5 mg of alendronate with 0.5 μg of calcitriol was effective in preventing bone loss and enhancing bone density in postmenopausal Korean women.[22] Furthermore, Nakamura et al[23] reported that the combined treatment of alendronate and calcitriol improved bone density in ovariectomized (OVX) osteopenic rats, which were osteopenic due to estrogen deficiency.[23]

The results of Zhang et al's study also support the efficacy of calcium gluconate combined with calcitriol in elderly male patients with osteoporosis. This combination may increase BMD, improve bone metabolism, enhance bone turnover, and maintain a high safety profile over time.[24] Hu et al demonstrated that the combination of calcitriol and zoledronic acid in patients with diabetic osteoporosis following posterior cruciate ligament

Table 6

Comparison of bone mineral density in 2 groups of patients before and after treatment [$\bar{x} \pm s$].

		Femoral neck (g/cm²)		Lumbar spine (g/cm²)		Ward triangle (g/cm²)	
Group	N	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	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
Intervention	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		>.05	<.01	>.05	<.01	>.05	<.01

tibial attachment avulsion fractures of the knee resulted in significant improvements. These include enhanced BMD, improved bone metabolism indicators, pain relief, better knee joint function, and a reduced risk of refracture.[20]

From an inflammatory perspective, IL-1 is primarily produced by activated macrophages in response to inflammatory stimuli. Kielian et al[25] confirmed that both IL-1 and TNF-α play a crucial role in completely antagonizing osteoclast formation induced by inflammatory factors. This is largely because IL-1 mediates the process of TNF-α-induced osteoclastogenesis. Ohe et al[26] found that TNF-α influences osteoclasts through 2 pathways: firstly, by binding to TNF-α receptors, which promotes the secretion of IL-1, macrophage colony-stimulating factor (M-CSF), and the receptor activator of nuclear factor kappa-B ligand (RANKL). Möller et al[27] have confirmed that RANKL and TNF-α together enhance osteoclast formation. Simultaneously, TNF-α can inhibit osteoclast apoptosis, extending their survival. Secondly, TNF-α activates TGF-β, stimulating osteoclast formation following inflammation. T cells also play a critical role in IL-6 production. IL-6 promotes the expression of RANKL in osteoblasts and interacts with osteoclasts through TNF-α and IL-1.[28] Therefore, controlling the levels of IL-1, IL-6, and TNF-α is essential in the treatment of osteoporosis.

A significant decrease in the levels of IL-6, TGF-β1, and TNF-α and an increase in the level of IL-10 in the group treated with calcitriol along with bisphosphonates were among the important results of this study. These findings indicate that the combination therapy can effectively manage the condition and biochemical markers in patients with osteoporosis, leading to more positive outcomes. These findings have been corroborated by other studies. One study demonstrated that the combination of bisphosphonates and calcitriol significantly inhibited the levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), and transforming growth factor-β1 (TGF-β1).[29] In another study, levels of IL-1, IL-6, and TNF-α were significantly decreased in the combination therapy group at both 6 and 12 months posttreatment.[30]

Drug safety is a critical concern that must be carefully considered during the use and administration of medications. Overall, the combination of calcitriol and bisphosphonates has been found to be safe and beneficial for disease prognosis.[31] In the present study, the total incidence of side effects in the intervention group was lower than in the control group, although this difference was not statistically significant. The most common adverse reactions in the intervention group were dizziness and shivering. Similarly, the findings of Suh et al corroborated those of the present study, showing that the combination of alendronate and calcitriol does not lead to serious complications in patients. The overall adverse event rate in their study was 5.6%, with abdominal pain and indigestion being the most common adverse events.[32]

This study has some limitations that should be acknowledged. The study was conducted at a single center, limiting the generalizability of the findings to other settings with different patient populations and medical practices. Furthermore, the follow-up period was relatively short, with outcomes measured at only 1, 2, and 3 months. Osteoporosis treatments often require longer periods to fully assess their impact on BMD, pain, and functional improvement. The inclusion criteria were quite strict, excluding patients with various comorbidities, which limits the applicability of the results to a more diverse population. In addition, self-reported measures like the Visual Analogue Scale (VAS) for pain and the Barthel Index for daily living abilities may introduce variability and bias, as these outcomes are subjective and dependent on individual perception. Addressing these limitations in future research would help strengthen the findings and enhance their applicability.

5. Conclusion

In summary, calcitriol combined with bisphosphonates can significantly enhance the immune function of postmenopausal patients with OP, promote abnormal bone metabolism, increase BMD, reduce adverse reactions, and have high safety.

Author contributions

Data curation: Kui Han, Xiaoyan Wang.
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Methodology: Kui Han, Xiaoyan Wang.
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