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Original Article

The curative effect of the additional administration of ibandronate sodium and calcitriol on elderly patients with osteoporosis

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Abstract: Objective: This study explored the curative effect of ibandronate sodium and calcitriol capsules on the elderly undergoing osteoporosis treatment. Method: The retrospective analysis focused on 150 elderly patients with osteoporosis diagnosed in our hospital from July 2018 to June 2019. Using the random number grouping method, the patients were divided into the ibandronate sodium group (n=50), the calcitriol capsules group (n=50), and the combination group (n=50), respectively receiving the corresponding treatment. The efficacy of each group's treatment was compared. Results: The combination group showed higher lumbar vertebrae and hip bone mineral density (BMD) after 6 months and 12 months of treatment (P<0.05), lower pain scores after 3 months, 6 months, 9 months, and 12 months of treatment (P<0.05), and lower IL-1, IL-6, and TNF-α as well as TRAP-5b and BALP levels after treatment compared with the other two groups (P<0.05). The three groups showed no significant differences in their blood calcium or blood phosphorus levels after the treatment (P>0.05). The total response rate of the combination group was 96.00%, which was higher than the rate of 78.00% in the ibandronate sodium group and the rate of 80.00% in the calcitriol capsules group, respectively (P<0.05). Conclusion: With the additional administration of ibandronate sodium and calcitriol capsules, inflammation levels and pain levels are more effectively controlled and bone density is improved.

Keywords: Senile osteoporosis, ibandronate sodium, calcitriol capsules, inflammation levels, bone mineral density

Introduction

Osteoporosis occurs widely, and it is generally believed that an increase in bone resorption is the primary cause [1]. Osteoporosis often has a relatively long course and is often referred to as a 'silent' disease as the bone loss occurs progressively. Patients experience bone pain, with a higher risk of fractures compared with those without osteoporosis [2]. The aging population accounts for most of the burden, mainly because they lose so much bone mass with age, and their bone mass continues to decrease [3].

The pathological anatomy of osteoporosis patients shows a thinning bone cortex and osteoid layers, and a disproportionate loss of trabecular bone with high sparsity [4]. As to the affected population, in addition to the prevalence in the elderly, the incidence in women is also higher than that in men, especially among postmenopausal and elderly women. In recent years, the prevalence of osteoporosis has increased with the ageing of the population. Elderly patients with osteoporosis cannot tolerate surgical treatment, so they prefer conservative methods, and drugs are usually prescribed as the first line treatment.

Many studies have found that vitamin D supplements can increase bone density and reduce fracture risks. Calcitriol has been proven to be a vitamin D metabolite with the most obvious biological effect on bone and calcium metabolism. It can effectively prevent the decline of bone mass [5]. Ibandronate sodium is a third-generation nitrogen-containing bisphosphonate, which can effectively inhibit the formation of osteoclasts or induce osteoclasts apoptosis,

thus improving bone density and significantly reducing the risk of fractures [6]. This study recruited 103 elderly osteoporosis patients admitted in our hospital from July 2018 to June 2019, and specifically analyzed the performance of the above mentioned drugs to explore this new effective therapy.

Materials and methods

Baseline data

A retrospective analysis was performed on 150 elderly patients with osteoporosis diagnosed from July 2018 to June 2019 in our hospital. Using the random number table grouping method, the patients were divided into the ibandronate sodium group (n=50), the calcitriol capsules group (n=50), and the combination group (n=50). The patients in the ibandronate sodium group ranged in age from 60-83 years, and the duration of their osteoporosis ranged from 3-12 years; the patients in the calcitriol capsules group ranged in age from 60-84, years and the duration of their osteoporosis ranged from 3-13 years; the patients in the combination group ranged in age from 61-86, years and the duration of their osteoporosis ranged from 2-13 years. (1) Inclusion criteria: patients aged over 60 years, with primary osteoporosis diagnosed through a CT test; patients with no history of allergic reactions to drugs; patients who voluntarily signed the study's informed consent form. (2) Exclusion criteria: patients under 60 years old; patients with life-threatening conditions, such as serious heart, liver, kidney, or lung diseases; secondary osteoporosis; patients who have had allergic reactions to the drugs used in the study; patients who could not complete all the follow-ups. This study was approved by the Ethics Committee of Zhuji People's Hospital. Each of the study participants provided a written informed consent before participating in the study.

Methods

The patients in the ibandronate sodium group received ibandronate sodium (1 mg: 1 ml, H20010432, Hebei Medical University Biomedical Engineering Center). The patients were administered an ibandronate sodium injection (2 mg) diluted in 250 ml of 0.9% sodium chloride solution through an intravenous infusion. The infusion time was controlled to at least 2 hours, and the treatment was performed every 3 months, and lasted for one year, or 4 cycles.

The patients in the calcitriol capsules group received the treatment of calcitriol capsules (0.25 μg * 10 capsules, H20140597, Roche Pharma, Ltd., Switzerland). The patients were administered 2 capsules at a time, once a day, for 1 year.

The patients in the combination group received the treatment of ibandronate sodium and calcitriol capsules. The patients were administered an ibandronate sodium injection (2 mg) diluted in 250 ml of 0.9% sodium chloride solution through an intravenous infusion. The infusion time was controlled to at least 2 hours. Also, the patients were administered 2 capsules at a time, once a day, for 1 year.

Outcome measurement

(1) BMD: The lumbar spine and hip BMD were measured using GE Dual energy X-ray Absorptiometry (DXA) before the treatment, and at 6 months and 12 months after the treatment. The L2-4 vertebrae in the lumbar spine and the total femoral neck and the femur in the hip were examined. (2) Pain level: the Visual Analogue Scale (VAS) [7] was administered before the treatment, and at 3, 6, 9, and 12 months after the treatment The scale has possible scores ranging from 0 to 10, where 0 represents no pain at all, and 10 represents severe and unbearable pain. Higher scores indicate more severe pain. (3) Inflammation level: 5 ml of elbow vein blood in a fasting state was drawn before and at 12 months after the treatment, then centrifuged at 3000 rpm for 5 minutes. The upper serum was collected. The tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) levels were determined using ELISA. (4) Blood biochemical indicators: 5 ml elbow vein blood was taken, then centrifuged to obtain the upper serum as mentioned above. The tartrate resistant acid phosphatase (TRAP-5b) and bone alkaline phosphatase (BALP) levels were measured using ELISA. In the meantime, the calcium and phosphorus levels were measured with an automatic blood analyzer. (5) Curative effect definitions [8]: Cured: all the patient's symptoms completely disappeared after 1 year of treatment, and the patient's

Table 1. Comparison of the baseline data ($\bar{x}$ ± s)/[n (%)]

Index		Combination group (n=50)	Ibandronate sodium group (n=50)	Calcitriol capsules group (n=50)	t/X^2	*P*
Sex	Male	18 (36.00)	16 (32.00)	17 (34.00)	0.137	0.195
	Female	32 (64.00)	34 (68.00)	33 (66.00)		
Age (years)		72.13±6.96	73.61±7.02	71.95±6.99	1.274	0.215
Duration (years)		6.35±3.29	6.41±3.32	6.38±3.30	0.076	0.934
Weight (kg)		65.48±4.19	66.83±5.01	66.03±4.75	1.187	0.108
Height (cm)		163.39±12.52	165.49±13.72	164.72±13.07	0.653	0.274

bone density and bone mineral content returned to normal. Improved: the patient only showed minor symptoms after 1 year of treatment, and the bone density and bone mineral content were close to the normal levels. Ineffective: After 1 year of treatment, there are still obvious symptoms, and the symptoms have worsened since the initial treatment. Their bone density and bone mineral content are still abnormal. Response rate = (cure + improvement)/total patients.

Statistical methods

SPSS 22.0 was used for all the statistical analyses. The measurement data are shown as the means ± standard deviation. The data comparisons between the groups were performed using independent sample t tests. The count data were expressed as [n (%)] and examined using X^2 tests. The multi-point comparisons within a group were analyzed using ANVOA with hoc post F tests, and P<0.05 indicated that the difference was statistically significant.

Results

Baseline data

There were no significant differences in terms of the proportion of males and females, average ages, heights, weights, or the duration of the osteoporosis in the combination group, the ibandronate sodium group, and the calcitriol capsules group (P>0.05) (**Table 1**).

Comparison of BMD

There were no significant differences in the lumbar or hip BMDs in the three groups before the treatment (P>0.05). After 6 months of treatment, the lumbar BMDs of the ibandronate sodium, calcitriol capsules and combination groups were (0.79±0.06) g/cm^2, (0.77±0.05) g/cm^2, and (0.82±0.08) g/cm^2, respectively, and the hip BMDs in the three groups were (0.68±0.04) g/cm^2, (0.66±0.03) g/cm^2, and (0.72±0.05) g/cm^2, respectively. After 12 months of treatment, the lumbar BMDs of the ibandronate sodium, calcitriol capsules, and combination groups were (0.80±0.07) g/cm^2, (0.79±0.06) g/cm^2, and (0.85±0.08) g/cm^2, respectively, and the hip BMDs in the three groups were (0.70±0.04) g/cm^2, (0.69±0.03) g/cm^2, and (0.76±0.05) g/cm^2, respectively. The data indicate that after 6 months and 12 months of treatment, the lumbar and hip BMDs were increased significantly in the three groups, and the lumbar and hip BMDs in the combination group were significantly higher than they were in the ibandronate sodium and calcitriol capsules groups (P<0.05), but there was no significant difference between the ibandronate sodium and calcitriol capsules groups (P>0.05) (**Figures 1**, **2**).

Comparison of the pain levels

Before the treatment, the combination group scored (7.21±1.13) points, the ibandronate sodium group scored (7.26±1.15) points, and the calcitriol capsules group scored (7.23±1.13) points. After 3 months, the pain scores in the combination group, the ibandronate sodium group, and the calcitriol capsules group were (5.31±1.02) points, (6.29±1.10) points, and (6.32±1.12) points, respectively; After 6 months, the pain scores in the combination group, the ibandronate sodium group, and the calcitriol capsules group were (3.65±0.86) points, (4.57±0.93) points, and (4.60±0.95) points, respectively. After 9 months of treatment, the pain scores were (2.33±0.51) points in the combination group, (3.04±0.59) points in the ibandronate sodium group, and (3.02±0.58) points in the calcitriol capsules group. At 12 months, the pain scores were (1.75±0.36)

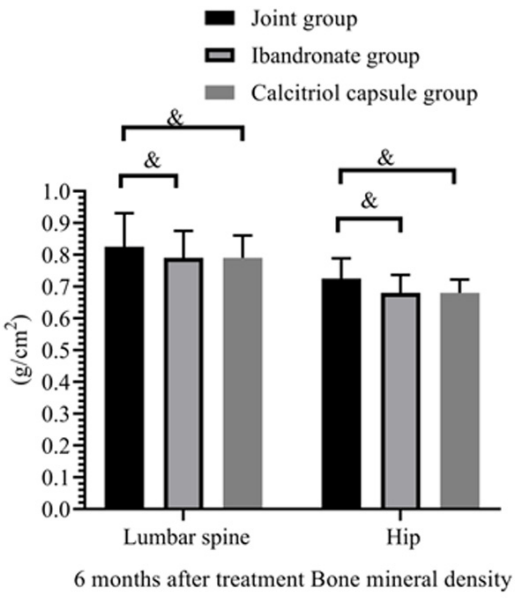

Figure 1. Comparison of the bone mineral density among the three groups after 6 months of treatment. After 6 months of treatment, the combination group showed higher lumbar spine and hip BMD than the other two groups (P<0.05). &indicates P<0.05 for inter-group comparisons.

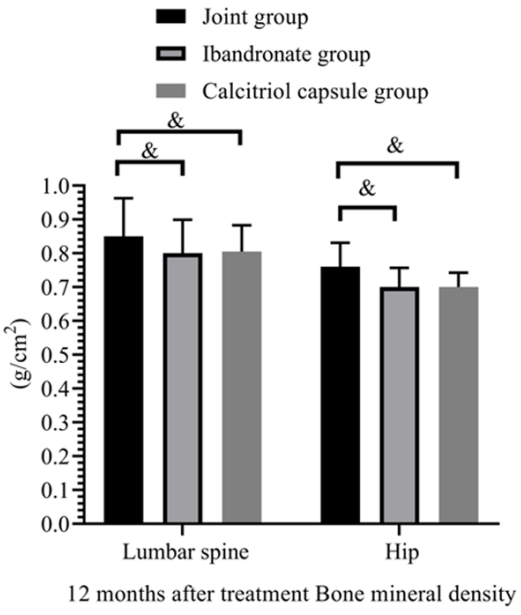

Figure 2. Comparison of the bone mineral density among the three groups after 12 months of treatment. The combination group showed higher lumbar spine and hip BMD than the other two groups (P<0.05). &indicates P<0.05 for inter-group comparisons.

points in the combination group, (2.67±0.40) points in the ibandronate sodium group, and

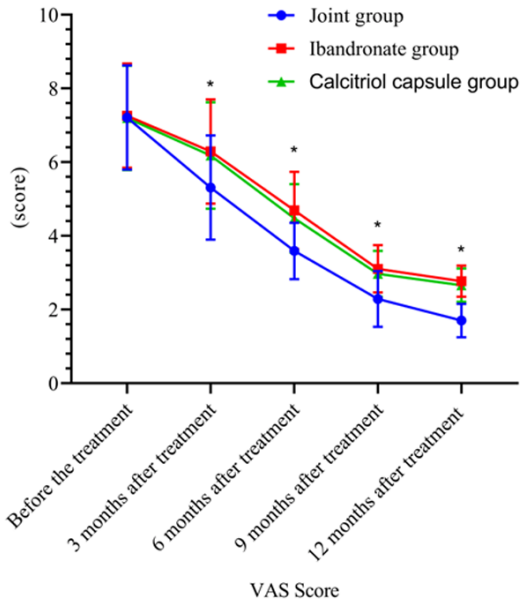

Figure 3. Comparison of the pain among the three groups. The three groups showed no significant differences in their VAS scores before the treatment (P>0.05). Compared with the ibandronate sodium group and the calcitriol capsules group, the combination group showed lower VAS scores after 3, 6, 9, and 12 months of treatment. #indicates the comparison of combination group and the other two groups, P<0.05.

(2.65±0.38) points in the calcitriol capsules group, respectively. Before the treatment, the pain scores of the three groups had no significant differences (P>0.05). The pain scores of the three groups gradually decreased from 3 months to 12 months after the treatment. The pain scores of the combination group were lower than the scores in the ibandronate sodium and calcitriol capsules groups at 3, 6, 9, and 12 months after the treatment (P<0.05), but there were no statistical differences between the ibandronate sodium and calcitriol capsules groups (P>0.05) (**Figure 3**).

Comparison of the inflammation levels

There was no significant difference in the levels of IL-1, IL-6 and TNF-α before the treatment in the three groups (P>0.05). After 12 months of treatment, the IL-1 levels in the combination group, ibandronate sodium group, and calcitriol capsules group were (0.17±0.05) ng/mL, (0.23±0.08) ng/mL, and (0.24±0.09) ng/mL; the IL-6 levels in the combination group, the ibandronate sodium group, and the calcitriol capsules group were (71.36±10.58) pg/mL,

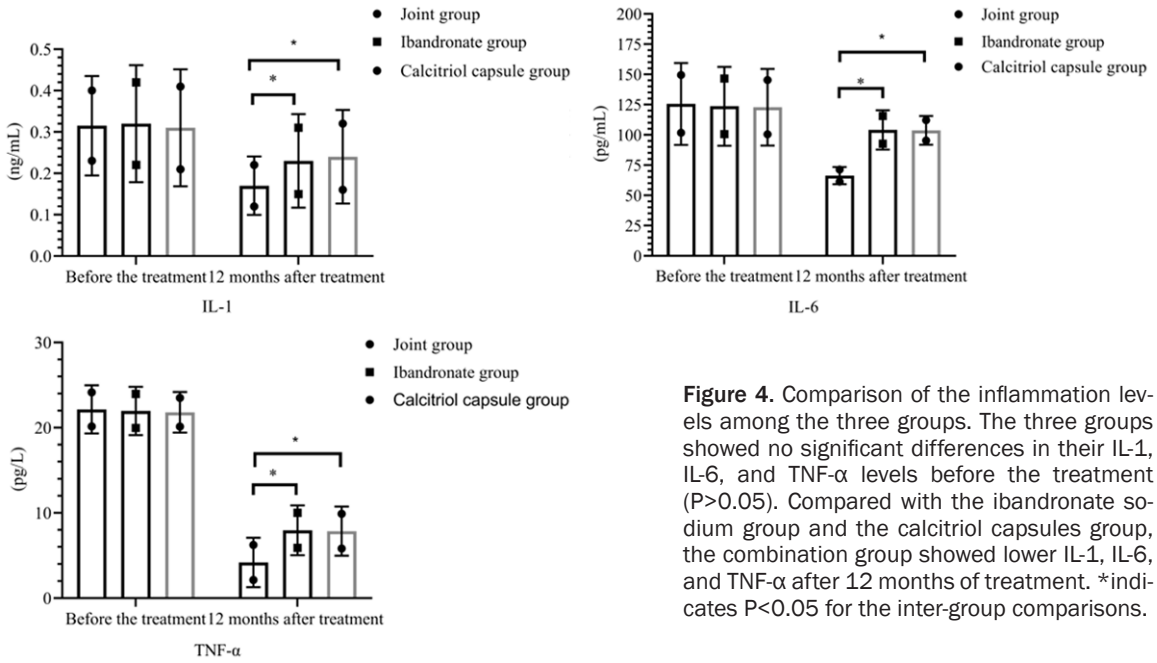

Figure 4. Comparison of the inflammation levels among the three groups. The three groups showed no significant differences in their IL-1, IL-6, and TNF-α levels before the treatment (P>0.05). Compared with the ibandronate sodium group and the calcitriol capsules group, the combination group showed lower IL-1, IL-6, and TNF-α after 12 months of treatment. *indicates P<0.05 for the inter-group comparisons.

Table 2. Comparison of the biochemical indexes ($\bar{x}$ ± s)

Grouping	Time points	Calcium (mmol/L)	Phosphate (mmol/L)	TRAP-5b (U/L)	BALP (U/L)
Combination group (n=50)	Before treatment	1.30±0.12	2.45±0.14	5.38±0.48	12.32±0.85
	After treatment	1.30±0.15	2.43±0.15	3.65±0.43	10.02±0.53
Ibandronate sodium group (n=50)	Before treatment	1.31±0.13	2.44±0.15	5.37±0.46	12.30±0.82
	After treatment	1.32±0.14	2.45±0.14	4.04±0.40	10.99±0.75
Calcitriol capsules group (n=50)	Before treatment	1.32±0.13	2.46±0.15	5.39±0.49	12.31±0.84
	After treatment	1.31±0.12	2.44±0.13	4.08±0.42	11.03±0.86
t		0.699	0.751	7.592	4.764
P		0.486	0.137	0.000	0.000

Note: t and P were the statistical values of the three groups after treatment.

(103.65±12.84) pg/mL, and (104.61±12.89) pg/mL; the TNF-α levels in the combination group, the ibandronate sodium group, and the calcitriol capsules group were (4.13±2.64) pg/L, (7.89±2.73) pg/L, and (7.92±2.75) pg/L. The IL-1, IL-6, and TNF-α levels in the combination group were significantly lower than the levels in the ibandronate sodium and calcitriol capsules groups after the treatment (P<0.05), but there was no statistical difference between the ibandronate sodium and calcitriol capsules groups (P>0.05) (**Figure 4**).

Comparison of the blood biochemical indicators

The blood calcium, phosphorus, TRAP-5b, and BALP levels were not significantly different in the three groups before the treatment (P>0.05). After the treatment, there was no significant difference in the levels of blood calcium and blood phosphorus in the three groups (P>0.05). However, after the treatment, the levels of TRAP-5b and BALP in the combination group were lower than the levels in the ibandronate sodium and calcitriol capsules groups (P<0.05), but there was no significant difference in the TRAP-5b and BALP levels between the ibandronate sodium and calcitriol capsules groups (P>0.05) (**Table 2**).

Comparison of the total response rates

Of the 50 patients in the combination group, the total response rate was 96.00%, which was significantly higher than the rate of 78.00% in

Table 3. Comparison of the total response rates [n (%)]

Grouping	Cure	Improvement	Ineffective	Response rate
Combination group (n=50)	20 (40.00)	28 (56.00)	2 (4.00)	48 (96.00)
Ibandronate sodium group (n=50)	17 (34.00)	22 (44.00)	11 (22.00)	39 (78.00)
Calcitriol capsules group (n=50)	16 (32.00)	24 (48.00)	10 (20.00)	40 (80.00)
X^2				4.158
P				0.039

the ibandronate sodium group and 80.00% in the calcitriol capsules group (P<0.05), but the total response rate showed no significant difference between the ibandronate sodium and calcitriol capsules groups (P>0.05) (**Table 3**).

Discussion

Studies on osteoporosis have always focused on calcium metabolism and the mechanical properties of bones. Both physiological and pathological factors will augment the lowering of calcium levels in bone tissue, leading to a larger pore size and worse mechanical properties, conditions which significantly increase the risk of fractures. The physiological factors usually include age and menopause in women, and the pathological factors are plentiful and include metabolism, inflammation, sports injuries, endocrine diseases, etc. [9, 10]. The WHO diagnostic criteria state that osteoporosis occurs when bone density is reduced by more than 2.5 from normal levels [11].

Medical studies have revealed that the composition of bone tissue includes osteocytes, osteoclasts, and osteoblasts, of which osteoblasts are involved in bone formation, and osteoclasts play a role in bone resorption. Bone formation and resorption occur simultaneously, that is, the metabolism of bone tissue [12]. During childhood, bone formation exceeds resorption, and eventually the circumferential lamella will be formed [13]. When the body enters adulthood, bone formation and bone resorption remain in a dynamic balance, leading to stable bone mass. In one's 30 s, the bones have reached their maximum strength and density, known as peak bone mass, and bone formation will be slow afterwards. Osteoporosis will occur at some point [14].

The principle of osteoporosis treatment is to control the reduction of bone mass, improve the patients' abilities in daily activities and their quality of life [15]. As the main treatment method, the choice of drugs is crucial. Ibandronate sodium is in the third generation of bisphosphonates and has a good affinity for skeletal hydroxyapatite, which can be used for bone binding activity. It could effectively inhibit osteoclast and control bone resorption [16].

Animal experiments conducted by Khlusov et al. [17] showed that osteoclasts can bind with large doses of ibandronate sodium, which can significantly reduce bone resorption and help gradually increase bone mass at bone reconstruction sites. In addition, Kucukzeybek et al. [18] found that after the ibandronate sodium was applied to the rat model, it loses pharmacological activity, and bone formation was detected on ibandronate sodium at 6 and 49 days. After the alendronate was combined with the bone, its pharmacological activity was gone. In order to effectively inhibit osteoclasts, the continuous administration of ibandronate sodium is a must. Although this drug showed outstanding effects, some studies have also confirmed its shortcomings, which are characterized by large molecular polarity, poor fat solubility, and difficulty in absorption via oral administration [19]. Other studies have found that this drug could irritate the esophageal mucosa after long-term use, limiting its clinical application.

Calcitriol capsules were often prescribed for osteoporosis treatment. Compared with ordinary vitamin D, it is the activated form of vitamin D and directly targets vitamin D receptors in tissues and organs. It exerts its effects quickly and has a short half-life [20]. Calcitriol capsules can effectively induce the formation of vitamin D receptors and increase the number and activity of vitamin D receptors, and they have a good therapeutic effect on vitamin D deficiency caused by vitamin D resistance. Obiol et al. [21] found that calcitriol capsules can not only be used in patients with vitamin D deficiency, but also in patients with normal levels of vitamin D.

In this study, the combination group received both drugs. The group exhibited higher lumbar spine and hip BMDs than the other two groups after 6 and 12 months of treatment (P<0.05), suggesting that the combination of two drugs was more effective in increasing the BMDs of patients with osteoporosis. The pain scores in the combination group after 3, 6, 9, and 12 months of treatment were lower than they were in the other two groups (P<0.05), suggesting that the combination of the two drugs can more effectively relieve pain caused by osteoporosis compared with one drug.

TRAP-5b is secreted by osteoclasts and shows enzymatic activity. Its level has a connection with the progression of osteoporosis [22]. Generally, the TRAP-5b level will increase during menopause and in climacteric males. However, osteoporosis can send the level even higher [23]. Therefore controlling TRAP-5b is crucial for osteoporosis treatment. BALP has always been considered an important indicator of early bone changes. The higher its level, the greater the degree of bone changes and the higher the risk of osteoporosis [24]. Therefore, controlling BALP could also decrease the severity of osteoporosis.

From the perspective of inflammatory levels, IL1 is mainly produced by activated macrophages in response to inflammatory stimuli. Kielian et al. [25] confirmed that both IL-1 and TNF-α play a pivotal role in completely antagonizing osteoclast formation caused by inflammatory factors. This is mainly due to the fact that IL-1 can mediate the process of TNF-α-induced osteoclasts. Ohe et al. [26] showed that TNF-α can act on osteoclasts using two pathways. On the one hand, it binds to TNF-α receptors, which promote 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 can jointly promote the formation of osteoclasts. At the same time, TNF-α can also inhibit the osteoclasts' apoptosis, leading to longer survival cycles. On the other hand, TNF-α can activate TGF-β and stimulate the formation of osteoclasts after inflammation.

T cells play a crucial role in the production of IL-6. IL-6 can promote the expression of osteoblasts' RANKL and act on osteoclasts through TNF-α and IL-1 [28]. Therefore, it is very important to control the levels of IL-1, IL-6, and TNF-α in in the treatment of osteoporosis. The total response rate in the combination group after treatment was higher than the other two groups (P<0.05). Also, the combination group showed lower levels of IL-1, IL-6, and TNF-α. After 12 months, the combination group exhibited higher TRAP-5b and BALP levels than the other two groups (P<0.05), suggesting that the combination of two drugs can effectively control the condition and the biochemical levels of patients with osteoporosis, and offer more positive results.

In summary, the combination of ibandronate sodium and calcitriol in the treatment of senile osteoporosis can more effectively control inflammation levels, reduce pain, and improve BMD. However, there were a small number of subjects included in this study. In addition, we did not explore the mechanisms of the drugs. In future studies, we will focus on larger sample sizes and conduct more in-depth research.

Disclosure of conflict of interest

None.

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