

# Management of osteoporosis with calcitriol in elderly Chinese patients: a systematic review

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**Abstract:** Osteoporosis, a skeletal disorder characterized by a reduction in bone strength, is becoming a major public health problem in the People's Republic of China, with a rapid increase observed among the population. Chinese guidelines particularly recommend use of active vitamin D in managing osteoporosis. 1,25-(OH)<sub>2</sub>D<sub>3</sub> (calcitriol) is an active vitamin D metabolite. It plays a role in many biological processes, especially in bone metabolism and muscle function, and is mediated by vitamin D receptors. Osteoporosis in elderly men and women is characterized by uncoupled bone remodeling, which is induced by sex hormone deficiencies, somatopause, vitamin D deficiency, reduced synthesis of D hormone, and lack of receptors or receptor affinity for D hormone in target organs. Reviewed here are six randomized controlled trials on calcitriol monotherapy and five on calcitriol therapy combined with other antiosteoporotic agents. Evidence from these trials shows that calcitriol monotherapy can improve bone mineral density in elderly osteoporotic Chinese patients but may be insufficient for long-term treatment. Calcitriol can also decrease bone turnover markers and bring about significant improvements in muscle strength. Further, calcitriol in combination with other therapeutic bone agents was shown to be well tolerated and capable of additional bone-preserving effects compared with use of calcitriol alone in areas including bone mineral density, bone turnover markers, bone pain improvement, and fracture incidence. Hypercalcemia and hypercalciuria, the most common side effects of calcitriol therapy, were not documented in the trials reviewed, and might have been the result of the low dosages used. One study showed that treatment with calcitriol can improve quality of life in patients with osteoporosis, although not to the same extent as bisphosphonates.

**Keywords:** osteoporosis, vitamin D, calcitriol, vitamin D receptor, review

## Introduction

Osteoporosis is a skeletal disorder characterized by diminished bone strength that can result in an increased risk of fracture. In 2006, among the segment of the Chinese population aged 50 years or older, 65 million people were considered to be osteoporotic, while an additional 213 million were estimated to have osteopenia.<sup>1</sup> Also, a recent study revealed a rapid increase in the incidence of hip fractures in the Beijing area.<sup>2</sup> In light of these severe public health challenges, the prevention and treatment of osteoporosis is of great importance in the People's Republic of China. The Chinese guidelines for diagnosis and management of osteoporosis<sup>3</sup> recommend both lifestyle intervention and medical treatment to prevent osteoporotic fractures. Calcium and vitamin D supplements are the essential steps that should be taken prior to embarking on medication. Based on the published evidence, bisphosphonates, calcitonin, hormonal replacement therapy, selective estrogen receptor modulators, strontium,

and parathyroid hormone are all recommended in the guidelines. According to the guidelines,<sup>3</sup> active vitamin D is recommended for osteoporotic patients who are elderly, have renal dysfunction, or have  $1\alpha$ -hydroxylase deficiency. Active vitamin D includes  $1\alpha$ -hydroxyvitamin D ( $1\alpha$ -calcitriol) and  $1,25$ -dihydroxyvitamin D (calcitriol). The latter, first approved for the treatment of osteoporosis by the China State Food and Drug Administration in 1992, is still widely used as an intervention for osteoporosis in the People's Republic of China. It is thus necessary to clarify the evidence surrounding the use of active vitamin D, in particularly calcitriol, in the Chinese population with osteoporosis.

## Physiological and pharmacological effects of calcitriol

$1,25(\text{OH})_2\text{D}_3$  is an active vitamin D metabolite. It is converted from  $25\text{-OH-D}_3$  by hydroxylase. Mediated by the vitamin D receptor (VDR),  $1,25(\text{OH})_2\text{D}_3$  plays an important role in many biological processes, including bone metabolism, muscle function, and the immune response. Although recent attention has been focused on the nonskeletal effects of vitamin D, it is well established that vitamin D is critical for bone metabolism.

It is uncertain whether  $1,25(\text{OH})_2\text{D}_3$  acts directly on bone or if it mediates its antirachitic effects indirectly by stimulation of intestinal absorption of calcium and phosphorus. Some studies have shown that differentiation of osteoblasts and osteoclastogenesis can be stimulated by  $1,25(\text{OH})_2\text{D}_3$ .<sup>4</sup> The effect of  $1,25(\text{OH})_2\text{D}_3$  on osteoclastogenesis is indirect, which requires cell-to-cell contact between osteoblasts and osteoclast precursors. When recognized by its receptor on osteoblasts,  $1,25(\text{OH})_2\text{D}_3$  can increase expression of receptor activator of NF $\kappa$ B ligand (RANKL), which binds RANK. RANK on the preosteoclast induces the preosteoclast to become a mature osteoclast.<sup>5</sup>  $1,25(\text{OH})_2\text{D}_3$  has also been reported to stimulate production of calcium-binding proteins, ie, osteocalcin and osteopontin, in osteoblasts. Runx2, a transcriptional regulator of osteoblast differentiation, is also regulated by  $1,25(\text{OH})_2\text{D}_3$ .<sup>4</sup> Transgenic mice overexpressing the VDR in osteoblastic cells show increased bone formation, which further indicates the direct effects of  $1,25(\text{OH})_2\text{D}_3$  on bone.<sup>6</sup> At the same time, from a physiological perspective, vitamin D can influence bone metabolism by providing calcium and phosphate through its effects on the gut, bone, and kidneys.  $1,25(\text{OH})_2\text{D}_3$  interacts with its specific nuclear VDR in the intestines to enhance the efficiency of intestinal absorption of calcium and phosphorus. In the kidneys, it affects calcium transport in the distal tubule by enhancing the action of parathyroid hormone and

by inducing transient receptor potential cation channel, subfamily V, member 5 and calbindins. Another important effect of  $1,25(\text{OH})_2\text{D}_3$  in the kidneys is inhibition of cytochrome P450 (CYP)27B1 ( $25\text{-OH-D}_3$   $1\alpha$ -hydroxylase) and induction of CYP24 ( $1,25\text{-OH}_2\text{-D}_3$   $24$ -hydroxylase).<sup>7</sup> Effects of  $1,25(\text{OH})_2\text{D}_3$  on reabsorption of sodium phosphate transporter b-mediated phosphate in the proximal tubule have also been suggested.<sup>8</sup> Depending on parathyroid hormone status and on experimental conditions,  $1,25(\text{OH})_2\text{D}_3$  has been reported to increase or decrease renal reabsorption of phosphate.<sup>6</sup>

The effects of vitamin D on muscle function were first shown by Birge and Haddad.<sup>9</sup> There are three ways in which vitamin D metabolites can affect muscle metabolism.<sup>10</sup> First, a VDR in skeletal muscle cells that specifically binds  $1,25(\text{OH})_2\text{D}_3$  can lead to a ligand-receptor interaction that results in a final transcription complex. This genomic pathway was found to influence muscle cell calcium uptake, phosphate transport across the muscle cell membrane, and phospholipid metabolism, as well as to mediate cell proliferation and subsequent differentiation into mature muscle fibers.<sup>11</sup> Second, there is evidence indicating that  $1,25(\text{OH})_2\text{D}_3$ , possibly through a vitamin D membrane receptor, acts directly on muscle cell membranes, resulting in enhanced calcium uptake within minutes, both through voltage-dependent calcium channels<sup>12</sup> and calcium release-activated calcium channels.<sup>13</sup> Finally, muscle strength appears to be influenced by the VDR genotype in muscle cells. In nonobese elderly women, a 23% difference in quadriceps strength and a 7% difference in grip strength were found between the bb and BB genotype of the VDR.<sup>14</sup>

Osteoporosis in elderly patients of both sexes is characterized by uncoupled bone remodeling. This uncoupling is induced by sex hormone deficiencies, by the so-called somatopause (growth hormone or insulin-like growth factor deficiency), by vitamin D deficiency, and, importantly, by reduced synthesis of D-hormone in the kidneys<sup>15</sup> and bones ( $1\alpha$ -hydroxylase deficiency).<sup>16</sup> It is also induced by lack of receptors or receptor affinity for D hormone in target organs<sup>17</sup> (gastrointestinal tract, bones, and parathyroid gland).<sup>18</sup> Inadequate  $1,25(\text{OH})_2\text{D}_3$  levels will lead to lower intestinal calcium absorption, so more calcium will be mobilized from the skeleton, resulting in increased bone resorption. Additionally, insufficient D hormone levels result in limited synthesis of bone matrix proteins that are released by osteoblasts. This limited synthesis of bone matrix proteins as well as the limited regulation of cytokines which are important for bone turnover exert a negative influence on bone mass and quality.<sup>19</sup> Consequently, treatment with  $1,25(\text{OH})_2\text{D}_3$  may be beneficial for osteoporotic patients, especially in the elderly population.

## VDR polymorphism and response to calcitriol

The biological responses to vitamin D are mediated by the VDR, which is a DNA-binding transcription factor. VDR generates an active signal transduction complex consisting of a heterodimer of the  $1\alpha,25(\text{OH})_2\text{D}_3$ -liganded VDR and an unoccupied retinoid X receptor. This complex is able to recognize vitamin D-responsive elements in the DNA sequence of genes regulated by vitamin D.<sup>20</sup> By recruiting complexes of either coactivators or corepressors, activated VDR modulates the transcription of gene encoding proteins that promulgate the traditional genomic functions of vitamin D, for example, signaling intestinal calcium and phosphate absorption to affect skeletal and calcium homeostasis. The *VDR* gene located on chromosome 12cen-q12 contains 11 exons, and spans approximately 75 kilobases of genomic DNA.<sup>21</sup> It has been suggested that it is one of the candidate genes for genetic control of bone mass. Allelic variants of the *VDR* gene, recognized by *Apal* (allele A/a C-A), *BsmI* (allele B/b G-A), *FokI* (allele F/f C-T), and *TaqI* (allele T/t T-C) restriction endonucleases, have been associated with bone mineral density (BMD) in many studies as well as with bone loss in elderly subjects.<sup>22</sup> There is racial diversity in the distribution of *VDR* gene polymorphism. In a study carried out by Zhang et al on *VDR* gene diversity in the People's Republic of China<sup>23</sup> that involved 426 postmenopausal women, data on the respective prevalence of bb, Bb, and BB genotypes in women of the following ethnicities was reported: Han (90.5%, 9.5%, and 0%), Kazak (38.1%, 55.56%, and 6.35%), Uyгур (69.67%, 26.23%, and 4.1%), and Mongolian (50%, 45.54%, and 4.46%). This uneven distribution may reflect either recruitment bias or survival bias. A study of 145 elderly men<sup>24</sup> evaluated the effects of the *VDR BsmI* gene on 1,25-dihydroxy vitamin D<sub>3</sub> levels. The authors found that bb genotype individuals had low vitamin D<sub>3</sub> levels in comparison with BB and Bb genotype individuals, although the results did not reach statistical significance. Studies of the effects of *VDR* polymorphisms with respect to vitamin D intake or treatment are limited. Morrison et al<sup>25</sup> conducted a study in 333 postmenopausal women from New Zealand who were given calcitriol 0.25  $\mu\text{g}/\text{day}$  plus calcium 1 g/day versus only calcium 1 g/day. This study showed significant interactions between the main effects of treatment and genotype ( $P=0.027$ ,  $P=0.029$ , and  $P=0.016$ , respectively, for the interaction term for models with *Apal*, *BsmI*, and *TaqI*). After 3 years, they found that the fracture incidence had decreased for the aaTT genotype and that the response

to calcitriol was better for the Aatt genotype. Data on the relationship between *VDR* polymorphisms and response to calcitriol treatment in elderly osteoporotic patients is still valid in the People's Republic of China.

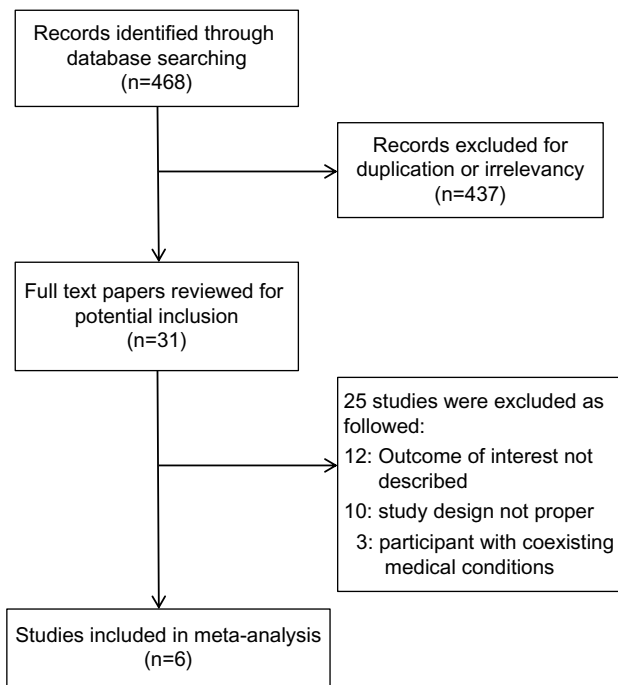
## Effect of calcitriol on BMD

We searched PubMed, EMBASE, and WanFang (<http://www.wanfangdata.com.cn>, a Chinese database) with article type restricted to clinical trials and publication time restricted to October 1, 2013 or earlier, using the following keywords: "calcitriol", "active vitamin D", "1,25(OH)<sub>2</sub>-vitamin D", "China", "Chinese", and "osteoporosis". Studies were included for review if the following conditions were met: they were randomized controlled trials; participants were patients with osteoporosis or bone loss; intervention consisted of use of calcitriol in the trial group and placebo or calcium in the control group; BMD as measured by dual-energy X-ray absorptiometry at the lumbar spine and femoral neck were collected as the primary outcome; and bone turnover markers were the secondary outcome. We excluded trials that enrolled participants with coexisting medical conditions (eg, diabetes). Statistical analyses were performed in Review Manager 5.2 (RevMan, version 5.2; The Cochrane Collaboration, Copenhagen, Denmark).

Initially, 468 relevant trials were identified. Following a preliminary review, 437 papers were excluded because of duplication or irrelevance. The remaining 31 trials were closely reviewed. Among them, 25 articles were excluded for the following reasons: outcome of interest not described ( $n=12$ ), improper study design ( $n=10$ ) and participants had coexisting medical conditions ( $n=3$ ). As a result, there were six trials included in the current meta-analysis (Figure 1).

The characteristics of the included studies are summarized in Table 1. All were randomized controlled trials that involved elderly males or females (mean age ranged from 56.3 years to 70.4 years) with bone loss. Subjects were randomly divided into calcitriol groups and control groups, receiving 0.25  $\mu\text{g}/\text{day}$  calcitriol plus one Caltrate D (600 mg of calcium and 125 IU of vitamin D; Pfizer Consumer Healthcare Company, Madison, NJ, USA) tablet daily, and one Caltrate D or placebo tablet daily, respectively. At 12 or 24 months, efficacy was mostly determined by BMD, bone turnover markers, muscle strength, and balance.

The BMD measurements for the six studies before and after treatment are shown in Tables 2 and 3. Combining available data at 12 months,<sup>26-30</sup> different BMD changes between control and trial groups were found (Figure 2) in spite of



**Figure 1** Diagram of literature search and selection.

heterogeneity. In the control groups, the BMD change was not significant and tended to be negative, while in the trial groups, BMD increased significantly. Available data for absolute BMD change (Figure 3) also points to significant preservation of lumbar spine and femoral neck BMD in the calcitriol groups. Some of these studies<sup>26,27</sup> recorded significantly higher percentage changes at the lumbar spine from baseline compared with control groups after adjusting for baseline difference. BMD change at the femoral neck ranged from being not significant<sup>26,28</sup> to significant.<sup>27,29</sup> Thus, calcitriol may have a beneficial effect on BMD, especially at the lumbar spine, during 12 months of treatment. In one of the reviewed studies, which had a duration of 24 months and enrolled 300 post-menopausal women between the ages of 55 and 75 years, after 24 months of treatment with calcitriol 0.25 µg/day and one Caltrate D tablet daily, BMD at the lumbar spine, trochanter, and femoral neck all decreased slightly (from 0.970±0.184 g/cm<sup>2</sup> to 0.968±0.186 g/cm<sup>2</sup>, from 0.657±0.106 g/cm<sup>2</sup> to 0.644±0.108 g/cm<sup>2</sup> and from 0.724±0.083 g/cm<sup>2</sup> to 0.722±0.102 g/cm<sup>2</sup>, respectively). We also noticed that in some studies<sup>31–33</sup> that compared the efficacy of calcitriol monotherapy with calcitriol therapy combined with other antiosteoporotic agents, some calcitriol monotherapy groups showed no significant changes in BMD after treatment. These data suggest that using calcitriol monotherapy to treat osteoporosis in elderly patients may not provide sufficient benefits, especially as a long-term treatment.

**Table 1** General characteristics of the five studies on calcitriol monotherapy

Study	1 <sup>26</sup>		2 <sup>36</sup>		3 <sup>27</sup>		4 <sup>28</sup>		5 <sup>29</sup>		6 <sup>30</sup>	
	Trial	Control	Trial	Control	Trial	Control	Trial	Control	Trial	Control	Trial	Control
Subjects	74	76	150	150	56	60	60	60	54	54	63	63
Age, years (±SD)	70.4±3.6	70.4±3.9	63.73±5.49	64.44±6.58	65.14±5.36	66.09±5.92	56.6±3.47	56.3±3.16	59.47±2.90	60.50±2.70	65.9±12.3	65.9±12.3
Treatment	Calcitriol 0.25 µg/day + calcium 600 mg/day Female T score < -1.0	Calcium 600 mg/day	Calcitriol 0.25 µg/day + calcium 600 mg/day Female T score < -2.5	Calcium 600 mg/day	Calcitriol 0.25 µg/day + calcium 600 mg/day Female Post-menopausal > 1 year > 2 risk factors for osteoporotic fracture	Placebo 600 mg/day Male T score < -1.0	Calcitriol 0.25 µg/day + calcium 600 mg/day Male T score < -1.0	Calcium 600 mg/day	Calcitriol 0.25 µg/day + calcium 600 mg/day Male T score < -2.5	Calcium 600 mg/day	Calcitriol 0.25 µg/day + calcium 750 mg/day Male and female T score < -2.5	Calcium 750 mg/day
Sex	Female	Female	Female	Female	Female	Male	Male	Male	Male	Male	Male and female	Male and female
Inclusion	T score < -1.0	T score < -1.0	T score < -2.5	T score < -2.5	T score < -2.5	T score < -1.0	T score < -1.0	T score < -1.0	T score < -2.5	T score < -2.5	T score < -2.5	T score < -2.5
Duration	12 months	12 months	24 months	24 months	12 months	12 months	12 months	12 months	12 months	12 months	12 months	12 months
Outcome	BMD; bone turnover markers; strength and balance	BMD; bone turnover markers; strength and balance	BMD; bone turnover markers; strength and balance	BMD; bone turnover markers; strength and balance	BMD; bone turnover markers	BMD; bone turnover markers	BMD; bone turnover markers	BMD; bone turnover markers	BMD; bone turnover markers	BMD; bone turnover markers	BMD; bone turnover markers	BMD; bone turnover markers

**Note:** T score = (BMD – reference BMD)/standard deviation.

**Abbreviations:** BMD, bone mineral density; SD, standard deviation.

**Table 2** BMD changes at L2–4 in the five studies of calcitriol monotherapy

Study	Patients (n)	Pretreatment (g/cm <sup>2</sup> )	12 or 24 months (g/cm <sup>2</sup> )	Percentage change	Absolute change
Xia et al <sup>26</sup>					
Caltrate D	72	0.930±0.126	0.935±0.137 <sup>b</sup>	0.83±3.88	0.008±0.036
Calcitriol + Caltrate D	70	0.916±0.132	0.945±0.130 <sup>c,f</sup>	2.84±4.04	0.025±0.034
He et al <sup>36</sup>					
Caltrate D	150	0.928±0.106	0.933±0.121		
Calcitriol + Caltrate D	150	0.970±0.184	0.968±0.186		
Xie et al <sup>27</sup>					
Control	51	0.902±0.155	0.902±0.154	0.19±4.05	
Calcitriol + Caltrate D	47	0.907±0.130	0.959±0.131 <sup>c,f</sup>	5.94±4.62	
He et al <sup>28</sup>					
Caltrate D	58	0.76±0.12	0.71±0.13		
Calcitriol + Caltrate D	57	0.75±0.14	0.82±0.18 <sup>b,f</sup>		
Zhu et al <sup>29</sup>					
Caltrate D	49	0.75±0.02	0.74±0.02		-0.01±0.09
Calcitriol + Caltrate D	52	0.76±0.03	0.79±0.04 <sup>b,f</sup>		0.03±0.06
Yang et al <sup>30</sup>					
Caltrate D	63	0.74±0.03	0.75±0.04		0.01±0.05
Calcitriol + Caltrate D	63	0.73±0.04	0.84±0.05 <sup>c,f</sup>		0.11±0.17

**Notes:** 12 or 24 months denotes 12<sup>26–30</sup> or 24<sup>36</sup> months after treatment. Values are expressed as the mean ± standard deviation. <sup>b</sup>P<0.05. <sup>c</sup>P<0.01 versus baseline by paired t-test. <sup>f</sup>P<0.01 compared between two groups by analysis of covariance adjusted for baseline BMD.

**Abbreviation:** BMD, bone mineral density.

## Effects of calcitriol in combination with other antiosteoporotic agents

Studies have shown that calcitriol can be well tolerated in combination with many kinds of antiosteoporotic agents, including bisphosphonates, calcitonin, hormonal

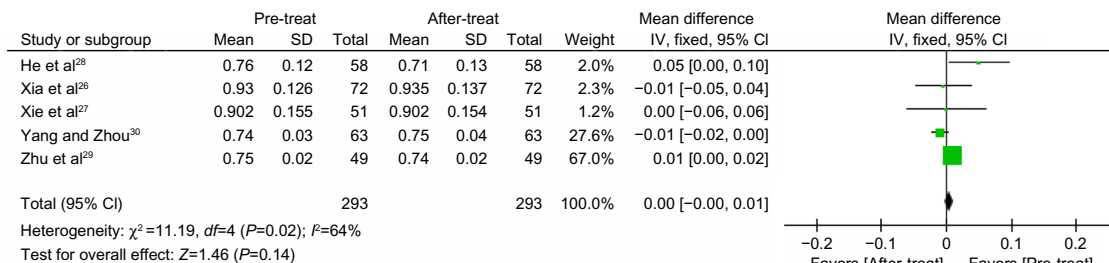
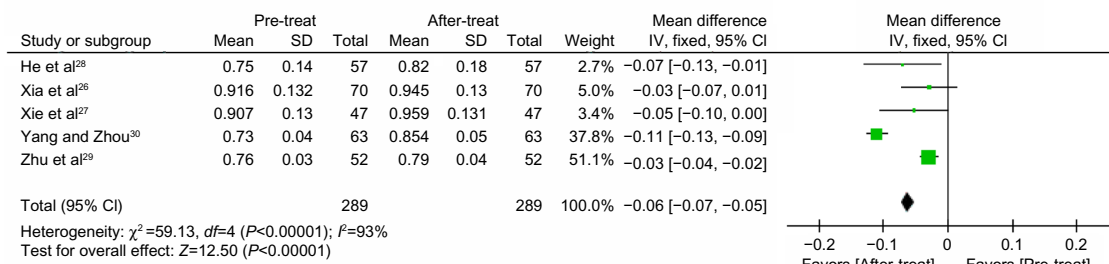
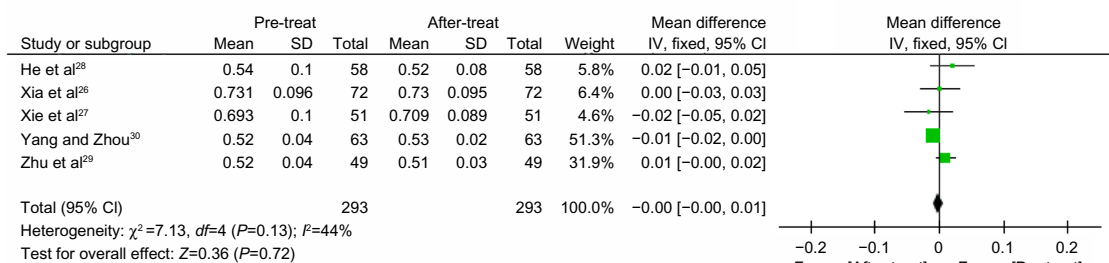
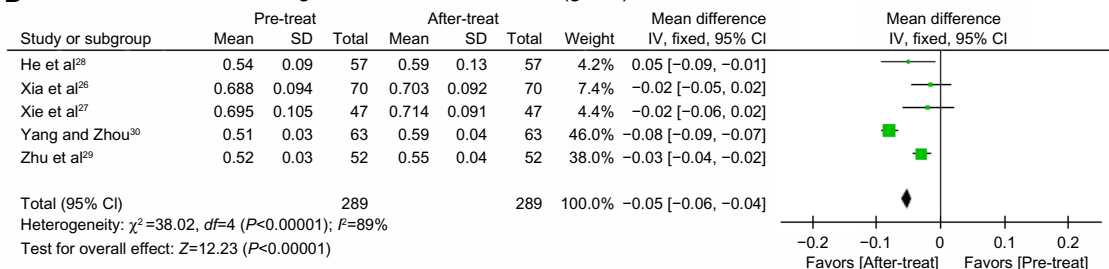
replacement therapy, selective estrogen receptor modulators, and traditional Chinese medicine. We searched PubMed, EMBASE, and WanFang for articles containing the keywords “China”, “Chinese”, and “osteoporosis”, and abstracts including “calcitriol”. Randomized controlled trials were included

**Table 3** BMD changes at the femoral neck in five studies of calcitriol monotherapy

Study	Patients (n)	Pretreatment (g/cm <sup>2</sup> )	12 or 24 months (g/cm <sup>2</sup> )	Percentage change	Absolute change
Xia et al <sup>26</sup>					
Caltrate D	72	0.731±0.096	0.730±0.095	0.04±3.94	0.000±0.029
Calcitriol + Caltrate D	70	0.688±0.094	0.703±0.092 <sup>c</sup>	2.01±5.45	0.012±0.037
He et al <sup>36</sup>					
Caltrate D	150	0.753±0.090	0.726±0.073		
Calcitriol + Caltrate D	150	0.724±0.083	0.722±0.102		
Xie et al <sup>27</sup>					
Control	51	0.693±0.100	0.709±0.089	-0.03±4.40	
Calcitriol + Caltrate D	47	0.695±0.105	0.714±0.091 <sup>b</sup>	3.43±10.34	
He et al <sup>28</sup>					
Caltrate D	58	0.56±0.10	0.52±0.08		
Calcitriol + Caltrate D	57	0.54±0.09	0.59±0.13 <sup>b,f</sup>		
Zhu et al <sup>29</sup>					
Caltrate D	49	0.52±0.04	0.51±0.03		-0.01±0.12
Calcitriol + Caltrate D	52	0.52±0.03	0.55±0.02 <sup>b,f</sup>		0.03±0.06
Yang et al <sup>30</sup>					
Caltrate D	63	0.52±0.04	0.53±0.02		0.01±0.05
Calcitriol + Caltrate D	63	0.51±0.03	0.59±0.04 <sup>c,f</sup>		0.08±0.12

**Notes:** 12 or 24 months denotes 12<sup>26–30</sup> or 24<sup>36</sup> months after treatment. Values are expressed as the mean ± standard deviation. <sup>b</sup>P<0.05. <sup>c</sup>P<0.01 versus baseline by paired t-test. <sup>f</sup>P<0.01 compared between two groups by analysis of covariance adjusted for baseline BMD.

**Abbreviation:** BMD, bone mineral density.

**A** L2-4 BMD change for caltrate D groups (g/cm<sup>2</sup>)**B** L2-4 BMD change for calcitriol + Caltrate D (g/cm<sup>2</sup>)**C** Femoral neck BMD change for Caltrate D groups (g/cm<sup>2</sup>)**D** Femoral neck BMD change for calcitriol + Caltrate D (g/cm<sup>2</sup>)

**Figure 2** BMD change at L2–4 and the femoral neck. Pooled estimate for the BMD change after 12 months of treatment with Caltrate D at L2–4 (**A**), calcitriol + Caltrate D at L2–4 (**B**), Caltrate D at the femoral neck (**C**) and calcitriol + Caltrate D at the femoral neck (**D**).

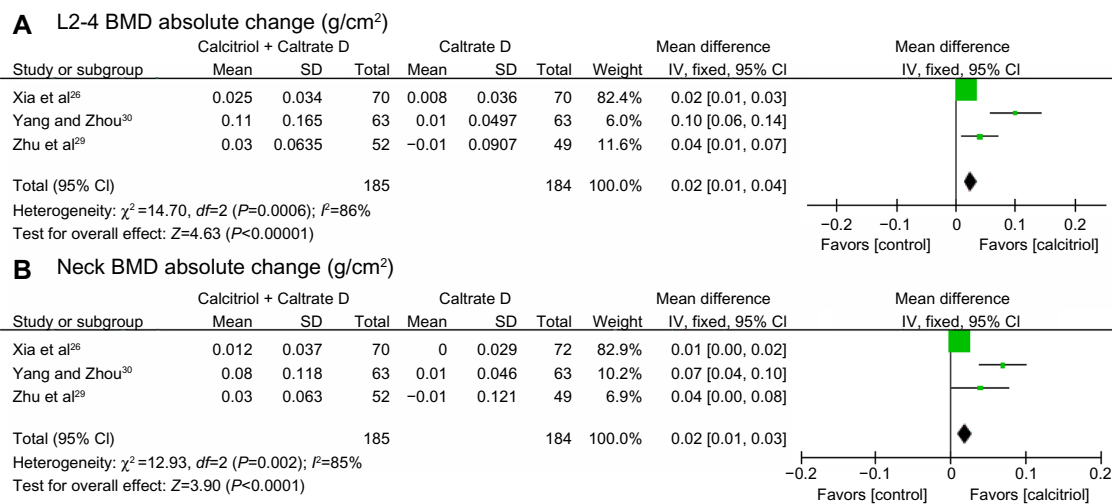
**Notes:** Boxes denote estimated mean differences; bars show 95% CIs; diamond indicates pooled mean differences; and the width of the diamond indicates pooled CIs.

**Abbreviations:** L2–4, lumbar vertebrae 2–4; CIs, confidence intervals; BMD, bone mineral density; SD, standard deviation; pre-treat, pretreatment; after-treat, after treatment; IV, inverse variance.

if they met the following criteria: participants were patients with osteoporosis; the subject number was more than 100; the intervention consisted of calcitriol monotherapy and calcitriol therapy in combination with other antiosteoporotic agents; and outcomes included BMD change, bone fracture, bone pain, or bone turnover markers. The search strategy retrieved 151 unique citations. Of these, 119 were excluded following initial screening based on abstracts or titles. After full-text review, five of the 32 remaining studies met the inclusion criteria (Table 4). Of the five trials selected, three involved

bisphosphonates, two involved calcitonin, and one involved hormonal replacement therapy.

Evidence presented by the trials suggested that combination therapy could decrease the incidence of bone fracture. Liu et al<sup>31</sup> carried out a 3-month study on 345 patients with previous osteoporotic vertebral compression fractures; 192 subjects in the trial group received salmon calcitonin (50 IU/day for the first week, 50 IU every 2 days after the first week) and oral calcitriol capsules (0.25 µg calcitriol three times a day), while 153 subjects in the control group received



**Figure 3** Absolute BMD change at L2–4 and the femoral neck. Pooled estimate for the difference in absolute BMD change after 12 months of treatment with Caltrate D or Caltrate D + calcitriol at L2–4 (**A**) and the femoral neck (**B**).

**Notes:** Boxes denote estimated mean differences; bars show 95% CIs; diamond indicates pooled mean differences; and the width of the diamond indicates pooled CIs.

**Abbreviations:** L2–4, lumbar vertebral levels 2–4; CIs, confidence intervals; NECK, femoral neck; BMD, bone mineral density; SD, standard deviation; IV, inverse variance.

oral calcitriol capsules (0.25  $\mu\text{g}$  calcitriol three times a day) only. The results indicated that salmon calcitonin and calcitriol combination therapy can decrease the incidence of subsequent fracture, which was 12% in the salmon trial group and 27.5% in the control group. An open study was carried out by Xuan et al<sup>32</sup> in 567 women with postmenopausal osteoporosis who were given calcitriol 0.25  $\mu\text{g}/\text{day}$  alone and calcitriol 0.25  $\mu\text{g}/\text{day}$  in combination with zoledronic acid 5 mg/year or tibolone 2.5 mg/day (a hormone replacement drug). This study showed that combination therapy can reduce the risk of new vertebral fracture by 61.9% (4.3% in the zoledronic acid and calcitriol group versus 12.6% in the calcitriol group) and 48.4% (6.5% in the tibolone and calcitriol group versus 12.6% in the calcitriol group) over a 2-year period.

Several studies have focused on improvement of bone pain following combination therapy. Wang<sup>33</sup> conducted a 6-month study in 320 osteoporotic patients and showed that bone pain was significantly improved in the trial group (alendronate 70 mg/week plus calcitriol 0.25  $\mu\text{g}/\text{day}$ ) compared with the control group (calcitriol 0.25  $\mu\text{g}/\text{day}$ ), with a verbal rating scale score for pain decreasing from  $1.79 \pm 0.42$  to  $0.92 \pm 0.18$  ( $P < 0.05$ ) in the trial group and from  $1.82 \pm 0.38$  to  $1.68 \pm 0.48$  in the control group. A randomized controlled trial reported by Miao<sup>34</sup> also showed a more significant pain improvement percentage in the trial group (zoledronic acid 5 mg/year, calcitriol 0.25  $\mu\text{g}/\text{day}$ ) than in the control group (calcitriol 0.25  $\mu\text{g}/\text{day}$ ).

All of the studies reviewed in this section showed that calcitriol in combination with other therapeutic bone agents

resulted in significant preservation of BMD compared with control treatments (Table 5). The gains in BMD from combination therapy could be related to synergistic bone-preserving mechanisms such as simultaneously decreasing bone resorption and increasing bone formation.<sup>35</sup> As a result, we can conclude that calcitriol in combination with other therapeutic bone agents may exert beneficial effects on reduction of fracture risk and bone pain as well as on increments of BMD in osteoporosis treatment.

## Effects of calcitriol on bone turnover markers

Biomarkers measured included nonspecific biomarkers, such as alkaline phosphatase, as well as specific markers, such as bone-specific alkaline phosphatase and gamma-carboxyglutamic acid-containing protein for bone formation and tartrate-resistant acid phosphatase for bone resorption. Bone turnover data are summarized in Table 6. After treatment in calcitriol monotherapy trials,  $\beta$  C-terminal telopeptide<sup>36</sup> alkaline phosphatase,<sup>37</sup> bone-specific alkaline phosphatase,<sup>28,29</sup> and tartrate-resistant acid phosphatase<sup>28,29</sup> were found to be significantly decreased in patients treated with calcitriol and increased in controls. Gamma-carboxyglutamic acid-containing protein was increased in both the calcitriol and control groups, although the results were not significant.<sup>27</sup> Of the five studies that focused on calcitriol in combination with other therapeutic bone agents, three reported significant changes in biomarkers such as bone-specific alkaline phosphatase, terminal C-telopeptide of collagen type I, and tartrate-resistant acid phosphatase that favored the calcitriol

Table 4 General characteristics of the combination therapy studies

Study Group	Wang <sup>33</sup>		Pei et al <sup>44</sup>		Miao <sup>34</sup>		Liu et al <sup>31</sup>		Xuan et al <sup>32</sup>		
	Trial	Control	Trial	Control	Trial	Control	Trial	Control	Trial 1	Trial 2	Control
n	160	160	32	88	55	55	192	153	185	190	192
Age, years ±SD	74.5	67.34±7.12	67.34±7.12	69.11±9.04	67.5	68.3	72.4±4.8	71.2±4.2	57.2±2.7	57.1±2.6	57.2±2.8
Treatment	Alendronate 70 mg/week + calcitriol 0.25 µg/day	Calcitriol 0.25 µg/day	Alendronate 70 mg/week + calcitriol 0.25 µg/day	Calcitriol 0.25 µg/day	Zoledronic acid 5 mg/year + calcitriol 0.25 µg/day	Calcitriol 0.25 µg/day	Salmon calcitonin 50 IU/day for the first week, 50 IU every two days after the first week + calcitriol 0.25 µg three times a day	Calcitriol 0.25 µg three times a day	Zoledronic acid 5 mg/year + calcitriol 0.25 µg/day + calcium 600 mg/day	Tibolone 2.5 mg/day + calcitriol 0.25 µg/day + calcium 600 mg/day	Calcitriol 0.25 µg/day + calcium 600 mg/day
Sex	Male/female	Female	Female	Female/male	Female/male	Female/male	Female/male	Osteoporotic vertebral compression fracture	Female	BMD; bone fracture; bone turnover markers	BMD; bone fracture; bone turnover markers
Inclusion	T score < -2.5	T score < -2.5	T score < -2.5	T score < -2.5	T score < -2.5	T score < -2.5	T score < -2.5	T score < -2.5	T score < -2.5; post-menopausal for 5–10 years	T score < -2.5; post-menopausal for 5–10 years	T score < -2.5; post-menopausal for 5–10 years
Duration	6 months	12 months	12 months	12 months	12 months	12 months	3 months	3 months	24 months	24 months	24 months
Endpoint	BMD; bone pain improvement	BMD	BMD	BMD, bone pain improvement; serum calcium and phosphate	BMD, bone pain improvement; serum calcium and phosphate	BMD, bone pain improvement; serum calcium and phosphate	BMD; bone pain improvement; bone turnover markers	BMD; bone pain improvement; bone turnover markers	BMD; bone fracture; bone turnover markers	BMD; bone fracture; bone turnover markers	BMD; bone fracture; bone turnover markers

Note: T score = (BMD – reference BMD)/standard deviation.

Abbreviations: BMD, bone mineral density; SD, standard deviation.

combination arm.<sup>31,32,34</sup> This evidence suggests that calcitriol may have suppressive effects on bone turnover.

## Effects of calcitriol on muscle strength and performance

Only two studies concentrated on muscle strength and performance as a response to calcitriol treatment in Chinese patients with osteoporosis. Muscle strength was evaluated by the stand and maximal forward reach test and five times sit-to-stand test, as well as by testing grip strength. In the study conducted by Xia et al,<sup>26</sup> left hand grip strength was significantly decreased in both groups following 6 months of treatment, although this change was not found after 12 months. At the same time, there were no significant changes in right hand grip strength observed in either group during the 12 months of treatment. The five times sit-to-stand test time decreased significantly from baseline in the control group but not in the calcitriol group, a difference the authors suggested may have been related to individual differences. The stand and maximal forward reach test time increased significantly in both groups. The other study found grip strength increased in both calcitriol and control groups following treatment.<sup>36</sup> These data indicate that treatment with Caltrate D alone or a combination of calcitriol and Caltrate D may have beneficial effects on muscle strength in elderly Chinese women.

## Quality of life

Quality of life scores for patients with osteoporosis are low, according to a study reported by Xu et al.<sup>37</sup> Guo et al<sup>38</sup> investigated the factors affecting quality of life in osteoporotic patients. Their subjects were 188 post-menopausal Chinese women aged 45–78 years with osteoporosis. Thirty-eight patients received no treatment on account of mild symptoms, and the remaining patients were randomly divided into three groups, ie, a bisphosphonate group, a calcium and calcitriol group, and a hormone replacement treatment group. Thirty-three factors, including treatment, general condition, health habits, and biological index were analyzed. Quality of life scores were measured before treatment and 3 and 12 months later using the Osteoporosis Quality of Life Scale developed by the Medical Outcome Evaluation for Gerontology research group.<sup>39</sup> This scale has 75 items and spans dimensions including disease, physiology, psychology, sociology, and patient satisfaction. The results showed that all three treatments, ie, bisphosphonate, calcitriol, and hormonal replacement therapy, can improve quality of life, with bisphosphonate being the most effective. Other significant factors included milk intake, smoking, alcohol use, age, physical work,



**Table 5** BMD changes in the four studies with calcitriol therapy in combination with other antiosteoporotic agents

Study	Patient (n)	Time (months)	L2–4 BMD (g/cm <sup>2</sup> )		Femoral neck BMD (g/cm <sup>2</sup> )	
			Pretreatment	After treatment	Pretreatment	After treatment
Wang <sup>33</sup>						
Calcitriol	160	6	0.821±0.092	0.830±0.086	0.742±0.094	0.752±0.104
Calcitriol + alendronate	160	6	0.819±0.117	0.902±0.112 <sup>b,f</sup>	0.740±0.098	0.812±0.112 <sup>b,f</sup>
Pei et al <sup>44</sup>						
Calcitriol	88	12	0.763±0.098	0.742±0.095 <sup>b</sup>	0.637±0.073	0.601±0.078 <sup>b</sup>
Calcitriol + alendronate	32	12	0.729±0.122	0.743±0.129 <sup>b,f</sup>	0.599±0.086	0.635±0.112 <sup>b,f</sup>
Miao <sup>34</sup>						
Calcitriol	55	12	0.723±0.176	0.752±0.163 <sup>b</sup>		
Calcitriol + zoledronic acid	55	1	0.725±0.201	0.858±0.198 <sup>c,f</sup>		
Liu et al <sup>31</sup>						
Calcitriol	153	3	0.79±0.10	0.81±0.12		
Calcitriol + calcitonin	192	3	0.80±0.09	0.88±0.11 <sup>b,f</sup>		

**Notes:** Values are expressed as the mean ± standard deviation. <sup>b</sup>*P*<0.05. <sup>c</sup>*P*<0.01 versus baseline by paired *t*-test. <sup>f</sup>*P*<0.01 compared between two groups by analysis of covariance adjusted for baseline BMD.

**Abbreviations:** BMD, bone mineral density; L2–4, lumbar vertebral levels 2–4.

and body mass index. Lian et al<sup>40</sup> conducted a controlled clinical trial in 282 post-menopausal Chinese women with osteoporosis. The subjects were divided into three treatment groups, ie, calcitriol, calcitriol plus calcitonin, and calcitriol plus ibandronate. All patients were followed up for one year. The results indicated that calcitriol alone does not improve quality of life significantly unless combined with calcitonin or ibandronate, indicating that post-menopausal osteoporosis should be treated with combined therapy.

### Safety and tolerability

Overdose of calcitriol may result in hypercalcemia, hypercalciuria, and hyperphosphatemia. Studies in Western countries have shown that hypercalcemia is present with calcitriol therapy in up to 40% of cases<sup>35</sup> and suggest that calcitriol, when used in higher doses, should not be combined with calcium supplementation. However, in all of the aforementioned Chinese studies, mild or no side effects of this type were found. Serum calcium and phosphorus concentrations were normal during the studies. No renal lithiasis or calcification was detected by ultrasound examination at the end of treatment. The small incidence of hypercalcemia may be due to the low doses used in Chinese patients, which is recommended at 0.25 µg/day. This also suggests that low doses of calcitriol combined with calcium supplementation may be safe for use in the elderly Chinese population. At the same time, it is still necessary to monitor serum calcium and phosphorus levels, urinary calcium excretion, and parathyroid hormone for the purpose of adjusting the medication dosage.<sup>41</sup> In one study combining calcitriol and alendronate,<sup>42</sup> serum calcium levels decreased

in the calcitriol plus alendronate group after 6 months, while serum calcium levels were found to be elevated in the calcitriol group. Although not significant, this result suggests that coadministration of a bisphosphonate can attenuate the risk of hypercalcemia during treatment with calcitriol. This finding is also consistent with that of a previous experiment wherein higher doses of a vitamin D hormone analog were used in combination with alendronate without increased hypercalcemia.<sup>43</sup> Calcitriol increases inorganic phosphate levels in serum, so caution is advised in patients with renal failure because of the danger of ectopic calcification. Serum phosphorus increased significantly in one of the studies<sup>36</sup> (*P*<0.05), but values remained within the normal range.

Patient withdrawal generally occurred due to gastrointestinal side effects,<sup>27–29,36,44</sup> including abdominal distention and constipation, which were thought to be caused by Caltrate D. No significant differences in markers of hepatic and renal function were recorded. No deaths or life-threatening toxicities were reported in any of the studies reviewed. Overall, tolerability of calcitriol was good.

### Limitations of this review

Some limitations were present in the Chinese studies that were reviewed here. First, although randomized, these studies were not double-blind. Investigators were blinded when interpreting dual-energy X-ray absorptiometry scans and bone turnover markers, but the subjects were not blinded because all the studies were open-label. Although this might not influence the main outcomes, such as BMD and bone turnover markers, it could have an influence on subjective assessments such as pain evaluations, thus introducing some amount of

**Table 6** Changes in bone turnover markers on calcitriol monotherapy or calcitriol therapy in combination with other antiosteoporotic agents

Study	Group	Patients (n)	Time, months	ALP (IU/L)		BSAP (U/L)		TRAP5b (U/L)	
				Pretreatment	After treatment	Pretreatment	After treatment	Pretreatment	After treatment
He et al <sup>36</sup>	Monotherapy								
	Caltrate D	150	12	98.12±27.55	82.81±22.73 <sup>c</sup>				
	Calcitriol + Caltrate D	150	12	94.31±26.72	76.68±18.75 <sup>cf</sup>				
Xie et al <sup>27</sup>	Caltrate D	56	12			48.88±22.81	50.69±24.23	5.16±1.74	5.26±1.78
	Calcitriol + Caltrate D	60	12			47.31±19.13	34.93±14.96 <sup>cf</sup>	5.29±2.01	3.25±1.75 <sup>cf</sup>
	Calcitriol + Caltrate D	54	12			47.10±19.10	49.68±23.12	5.18±1.78	5.24±1.68
Zhu et al <sup>29</sup>	Caltrate D	54	12			46.31±18.13	33.92±13.95 <sup>cf</sup>	5.30±2.02	3.18±1.62 <sup>cf</sup>
	Calcitriol + Caltrate D	54	12						
Miao <sup>34</sup>	Combination therapy								
	Calcitriol	55	12	157.1±14.6	152.6±13.7			5.88±1.37	5.97±1.39
Xuan et al <sup>32</sup>	Calcitriol + zoledronic acid	55	12	147.3±16.1	95.2±11.2 <sup>bf</sup>			5.89±1.42	2.10±0.37 <sup>cf</sup>
	Calcitriol	192	24					5.89±1.51	2.71±0.42 <sup>cf</sup>
	Calcitriol + zoledronic acid	185	24						
Liu et al <sup>31</sup>	Calcitriol + tibolone	190	24						
	Calcitriol	153	3	78.20±1.28	81.15±2.70 <sup>b</sup>				
	Calcitriol + calcitonin	192	3	77.90±1.48	78.08±2.12 <sup>f</sup>				

**Notes:** Values are expressed as the mean ± standard deviation. <sup>b</sup>*p*<0.05, <sup>c</sup>*p*<0.01 versus baseline by paired *t*-test. <sup>d</sup>*p*<0.01 compared between two groups by analysis of covariance adjusted for baseline BMD.

**Abbreviations:** ALP, alkaline phosphatase; BSAP, bone-specific alkaline phosphatase; TRAP5b, tartrate-resistant acid phosphatase 5b.

bias into the results. The second limitation was the small study sample sizes and the limited treatment periods. The longest duration among all of the studies was 24 months, and the results suggested that calcitriol monotherapy may be insufficient for long-term treatment of osteoporosis. Thus, the long-term effects and safety of calcitriol in elderly Chinese patients with osteoporosis still need to be explored. Finally, although some studies reported the incidence of fractures for calcitriol in combination with other antiosteoporotic agents, there were no studies that assessed fracture and fall incidence for calcitriol monotherapy, which is an important factor in evaluating the effectiveness of an antiosteoporotic drug. Above all, further double-blind studies with larger sample sizes as well as longer follow-up periods that assess bone fracture and fall incidence in addition to BMD and bone turnover markers are needed.

## Conclusion

In conclusion, calcitriol, which is mediated by VDR, plays a role in many biological processes, in particular bone metabolism and muscle function. The evidence suggests that calcitriol may reduce or even reverse BMD loss, decrease bone turnover markers, and improve quality of life in elderly Chinese patients with osteoporosis in short-term treatment with mild or no side effects. However, the long-term effects of calcitriol monotherapy may be unsatisfactory, and this is an area in need of further research. Calcitriol can be well tolerated in combination with various other therapeutic bone agents, and these combinations can exert more significant beneficial effects on reduction of fracture risk, improvement of bone pain, and BMD increment in osteoporosis treatment compared with calcitriol monotherapy.

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## Disclosure

The authors report no conflicts of interest in this work.

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