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The efficacy of calcitriol therapy in the management of bone loss and fractures: a qualitative review

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Abstract

Summary—Osteoporosis, a skeletal disorder characterized by a reduction in bone strength, increases fracture risk. Primary osteoporosis is usually a result of reduced bone mineral density as a consequence of natural aging. Secondary osteoporosis is usually a result of a disease, such as cystic fibrosis, or medical treatment, such as corticosteroids or cancer treatment.

Introduction—Currently, ten million Americans are osteoporotic and an additional 34 million have the precursor condition, osteopenia. Osteoporosis leads to 1.5 million fractures and 500,000 hospitalizations annually. Osteoporosis-related fractures increase mortality and reduce quality of life. Calcitriol, the active form of vitamin D, regulates intestinal calcium absorption, among other actions. During the past four decades, many clinical trials investigating the effect of calcitriol on bone loss have been performed.

Methods—We conducted a systematic qualitative review of clinical trials that assessed calcitriol for the treatment of osteoporosis and bone loss. In these clinical trials, calcitriol was used as a monotherapy and in combination with other therapeutic bone agents.

Results and conclusion—Studies using calcitriol monotherapy, although not conclusive, found that calcitriol slowed the rate of bone loss in a variety of populations. Calcitriol in combination with other therapeutic bone agents was shown to have additional bone-preserving effects when compared to the use of therapeutic bone agents alone. A common side-effect of calcitriol therapy was hypercalcemia and hypercalciuria, but the degree of hypercalcemia was mild. Recent research found that intermittent dosing can reduce hypercalcemia rates. Calcitriol, alone or in combination with other agents, should be considered for the therapy of osteoporosis.

Keywords

Bone biomarkers; Calcitriol; Clinical trials; Primary osteoporosis; Review; Secondary osteoporosis

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Conflicts of interest None.

Introduction

Osteoporosis is a skeletal disorder characterized by diminished bone strength, which results in an increased risk of fracture [1]. Unfortunately, there is no direct method of determining bone strength. The most commonly used measure of bone health is bone mineral density (BMD). Determining BMD through dual-energy X-ray absorptiometry (DXA) is considered the "gold-standard" for diagnosing osteoporosis, although it fails to detect half the cases of subsequent fractures [2]. Due to recent advances, relatively inexpensive biomarkers can be used to examine levels of bone turnover and predict the risk for osteoporosis. Markers of bone resorption measure levels of collagen breakdown products in blood or urine samples [1, 3, 4]. Levels of bone formation can also be determined fairly easily through blood tests that measure the proteins specific to formation [5].

Primary osteoporosis

Primary osteoporosis, the most common form, usually results from age-related reductions in bone mineral density and bone strength [6]. The disease is much more common in women who have a two- to threefold higher rate of osteoporosis than men [7]. The difference in osteoporosis rates is mainly due to the sudden drop in hormone levels that a woman experiences at the onset of menopause, during which rapid bone loss occurs for 4–8 years [8]. Over time, the body's capacity to form bone is reduced, and vitamin D and calcium intake tends to decline [1]. As serum levels of calcium decline, the body is forced to remove calcium from bone to make up for the deficit.

Secondary osteoporosis

Secondary osteoporosis is not related to aging. This type of osteoporosis is usually a side effect of another condition or medication. Those with secondary osteoporosis tend to lose bone at a greater rate than individuals of similar age, gender, and race. Several genetic diseases such as cystic fibrosis and Gaucher's disease have been linked to increased rates of osteoporosis, although these conditions are rare [9]. Osteoporosis can be caused by certain medications, most notably corticosteroids. Since corticosteroids are used to treat multiple conditions, corticosteroid-induced osteoporosis is a common form of secondary osteoporosis. Corticosteroids quickly reduce bone formation levels and increase bone resorption, resulting in a decreased BMD and increased risk of fracture [10, 11]. Other medications interfere with the absorption of compounds that are beneficial to bone health, such as calcium, vitamin D, and phosphate, often resulting in secondary osteoporosis [12].

Another cause of secondary osteoporosis is cancer treatment-induced bone loss. Over the past 25 years, advances in cancer treatment and screening have dramatically increased survival rates [13]. As a result, many people diagnosed with cancer are living longer, and currently more than ten million cancer survivors live in the United States [14, 15]. Unfortunately, many of these life-saving cancer treatments produce deleterious effects on the skeletal system. Several chemotherapeutic agents have direct effects on bone, resulting in reduced BMD [16, 17]. Additionally, chemotherapeutic drugs used for the treatment of lymphoma, breast, testicular, and prostate cancers often result in hypogonadism. The consequent drop in hormone levels results in rapid bone loss for these patients [18, 19]. Many breast and prostate cancers display some sort of hormone dependence for which endocrine therapies are employed [20, 21]. The use of these therapies, such as aromatase inhibitors and androgen deprivation therapy, leads to decreased BMD and increased risk of fracture [22–24]. Overall, many cancer survivors remain at risk for secondary osteoporosis.

Burden of osteoporosis

Currently, osteoporosis is a public health priority due to the large number of people affected. In 2004, ten million Americans were considered osteoporotic, while an additional 34 million were estimated to have the precursor condition, osteopenia [25]. Furthermore, the number of Americans with osteoporosis is expected to rise to almost 14 million women by the year 2020 [26]. This translates into 1.5 million fractures and leads to approximately 500,000 hospitalizations annually [27, 28]. Hip fractures are the most devastating; the risk of death is approximately three times higher for individuals in the year after a hip fracture, while the increased mortality from a vertebral fracture is less than two times higher [29, 30]. Additionally, about 20% of hip fracture patients require admission to a nursing home [31]. In addition to the increased morbidity due to osteoporosis, there is a financial burden placed on the medical system. It is estimated that expenditures related to osteoporosis fall just short of $18 billion annually [32]. Hip fractures account for the majority of cost, over 60%, and each hip fracture costs up to $40,000 in medical treatment [28, 32].

In addition to the considerable financial burden, there is also a detrimental effect on quality of life among individuals affected by osteoporosis. Approximately, two thirds of hip fracture patients do not return to their prefracture level of functioning [33]. Vertebral fractures often result in severe back pain that can last for years [34]. Osteoporosis-related fractures can limit daily activities, such as climbing stairs, getting dressed, cooking, and taking medications [35]. Fractures also have a profound effect on quality of life as measured by quality-adjusted life years [36]. Fracture patients also report significant sleep problems, depression, and fear of another fracture [37].

Vitamin D and vitamin D analogs

Plain vitamin D, often called native vitamin D, is photo-synthesized in the skin in response to sunlight or obtained from supplements or dietary sources. In humans, vitamin D is hydroxylated in the liver into the vitamin D analog alfacalcidol (1α-hydroxycholecalciferol), which is hydroxylated again in the kidney into the vitamin D analog calcitriol (1,25 dihydroxycholecalciferol). The advantage of administering vitamin D analogs is that the prodrug alfacalcidol avoids the effect of age-related declines in hepatic function, while calcitriol avoids the effect of age-related declines in hepatic and renal function [38]. However, due to their high potency, use of these vitamin D analogs is associated with a higher risk of hypercalcemia and hypercalciuria compared to native vitamin D supplementation, in addition to their higher cost [38, 39].

Scientists noted that calcitriol was responsible for the absorption of calcium from the intestine [40]. It was later hypothesized that calcitriol plays a crucial role in skeletal system regulation due to its effect on calcium absorption and may have additional bone-protective effects independent of its calcium absorption effects [41, 42]. In addition to its positive effects on the skeletal system, calcitriol plays a vital role in muscular function in which higher levels are associated with increased muscular strength and balance [43–45]. Although diminished BMD increases the risk of fracture, falls play an important role too [46, 47]. Reduced muscle strength and poor balance also enhance the risk of falls [48–51], and higher serum levels of calcitriol are associated with improved balance and strength [52–54]. Although this review focuses on bone metabolism and BMD, clinicians should also consider the nonskeletal benefits of calcitriol therapy when prescribing an antiosteoporotic regimen. During the past four decades, clinical trials have examined the efficacy of calcitriol in regard to bone loss, both as a monotherapy and in combination with other agents in different populations.

Methods

We performed a systematic review of the literature involving calcitriol therapy for bone loss. The following databases were searched in January 2009 for studies published between 1971 and 2009: Ovid/MEDLINE®, PubMed, and Cochrane. Two individuals independently searched these databases using the keywords calcitriol, vitamin D, cholecalciferol, 1,25 dihydroxyvitamin D, 1,25-dihydroxycholecalciferol, Rocatrol®, vitamin D analogs, and vitamin D hormone to identify clinical studies that used calcitriol. The following search terms: bone loss, bone mineral density, bone health, bone remodeling, bone turnover, bone, bone fractures, and fractures were used to identify clinical studies that assessed bone loss and/or bone metabolism. Articles identified as having used calcitriol and having assessed bone loss and/or bone metabolism were combined. Limits that were used included English language, clinical trial, and randomized controlled trials. Using the aforementioned search strategy, a total of 893 articles were identified, and Table 1 displays these results. Studies were included in this review if they (a) administered calcitriol and (b) examined the effect of calcitriol on either BMD or bone biomarkers. The primary author (L.J.P.) reviewed 893 abstracts of the identified articles to determine if they met the inclusion criteria for review. Publications that met the inclusion criteria were reviewed, and data such as the study population, design characteristics, primary results relevant to bone loss, assessment measures, and adverse events were recorded. The accuracy of the extracted information was confirmed by another author (S.H.). In addition, the references cited in the article that met the inclusion criteria were reviewed to identify additional trials that may not have been identified from the initial literature searches. Review articles and meta-analyses that examined the efficacy of vitamin D analog therapy in regard to bone health were identified but were not included, and the references from these articles were also reviewed to identify additional trials [38, 42, 54–61].

Monotherapy calcitriol therapy and bone biomarkers

Because detection of changes in bone mineral density can take years, short-term clinical trials must rely on other indicators of bone health such as biomarkers. Biomarkers of bone remodeling are classified according to their underlying processes and can be very accurate in predicting fracture risk [62]. The two distinct processes of bone remodeling are bone formation and bone resorption. While a decrease in bone resorption almost always indicates an improvement in bone health, interpreting changes in bone formation is not always so clear cut. Changes in bone formation are closely coupled with changes in bone resorption in which a change in bone formation is often a response to a change in bone resorption. A decline in bone formation can indicate increasing bone mineral density if levels of bone resorption have also declined, while an increase in bone formation may not necessarily mean an increase in BMD if bone resorption has increased during the same period. Interpreting changes in bone formation is most accurate when accompanied by changes in bone resorption. The most specific markers of bone formation include serum osteocalcin (OC) and bone-specific alkaline phosphatase (BSAP), and the most sensitive markers of bone resorption are crosslinked C- (CTx) and N- (NTx) telopeptides of type I collagen [63]. Older studies tended to rely on nonspecific biomarkers, such as total alkaline phosphatase (ALP) and urinary hydroxyproline (Hyp), which lack the sensitivity and specificity to accurately predict fracture risk [64].

Sixteen trials have examined the effect of calcitriol monotherapy on various bone biomarkers in healthy men, healthy women, and patients with primary or secondary osteoporosis [65–80]. Three trials examined the effects of calcitriol on bone biomarkers over a short period of time with two trials lasting 1 week [69, 77] and the other lasting 4 weeks [80]. All three of the studies found that levels of parathyroid hormone (PTH), a marker of

resorption, decreased significantly over the course of the study. Two of the studies reported statistically significant increases in bone formation, as determined by levels of OC [69, 77]. In addition, one study found that bone resorption, as determined by levels of NTx, significantly decreased over 4 weeks [80]. These studies demonstrated that a short course of calcitriol therapy was effective at stimulating bone formation and reducing bone resorption in a dose-dependent manner.

Nine trials have studied the effect of calcitriol on postmenopausal women, the majority of whom had already been diagnosed with osteoporosis [65–68, 70, 72–74, 79]. Trial durations ranged from 6 months to 8 years, with the majority lasting at least 1 year; the calcitriol doses ranged from 0.5 to 1.0 μg/day, with 0.5 μg/day as the most common dose. One study, a single-arm trial, reported a significant increase in bone formation from baseline to the completion of the study [66]. Of the seven studies that used a two-arm design and compared the effectiveness of calcitriol to a placebo or calcium therapy, four reported statistically significant increases in at least one bone biomarker in the calcitriol arm [67, 68, 73, 74]. The other three studies found no difference in women who were treated with calcitriol and the control groups for any of the bone biomarkers [65, 70, 72]. Two studies reported significant reductions in PTH levels, a marker of excessive bone resorption among those in the calcitriol arm when compared to the placebo group [73, 74]. Four studies reported significant reductions in bone resorption, [68, 73, 74, 79] and three studies reported significant changes in bone formation [66, 67, 74] for those in the calcitriol group compared to the control group. The final study used a three-arm design, comparing calcitriol therapy to hormone replacement therapy (HRT) and placebo among a group of early menopausal women and a separate group of 70-year old women [79]. No difference between calcitriol and placebo was noted among the early menopausal women, but 70-year old women in the calcitriol arm experienced a decline in bone resorption compared to the placebo group.

Four trials were identified that examined the effects of calcitriol among patients who underwent an organ transplant or received corticosteroid therapy [71, 75, 76, 78]. The trials lasted between 1 and 3 years, and the dose of calcitriol for these studies ranged from 0.25 to 0.75 μg/day. Two studies [71, 75] compared calcitriol therapy to placebo treatment, and one of those studies reported significant differences in levels of bone formation between the groups over the course of the trial in favor of the calcitriol arm [75]. One study compared the efficacy of calcitriol against the bisphosphonate alendronate [76] and the other trial compared calcitriol against HRT [78]. Both HRT and bisphosphonates have demonstrated bone-preserving effects; calcitriol demonstrated synergy when combined with HRT and equivalence when compared to bisphosphonates in regard to its ability to reduce bone resorption.

The majority of studies found monotherapy calcitriol was effective in reducing bone loss, as determined by various bone biomarkers, across a variety of populations, but the results should be interpreted with caution. Many of the older studies relied on nonspecific bone biomarkers such as Hyp and ALP, which are not as accurate at predicting bone loss as newer, more specific biomarkers [68, 70–73, 79]. In addition, the two studies that reported null results relied on nonspecific biomarkers [70, 72]. Among the 11 studies that used more specific biomarkers, all reported statistically significant changes in at least one of the markers, attesting to the effectiveness of calcitriol monotherapy to reduce levels of bone loss [65–67, 69, 74–78, 80]. Hypercalcemia was reported in six of the studies but was generally described as mild [65, 67, 72, 75, 76, 79]. Overall, the evidence suggests that calcitriol monotherapy is effective in improving bone metabolism, as determined by biomarkers, across a range of patient populations.

Monotherapy calcitriol therapy, BMD, and fractures

Measurements and changes in BMD are among the most predictive factors in determining fracture risk [81]. Nineteen trials examined the effect of calcitriol on changes in BMD across a variety of populations [65, 67, 70–72, 74–76, 78, 82–91]. BMD was assessed at various anatomical sites, including the hip, spine, femur, radius, and total body. Among these trials, the daily dose of calcitriol ranged from 0.25 to 1.0 μg, with 0.5 μg/day being the most common dose. The trial durations ranged from 6 months to 8 years; the majority of trials lasted between 1 and 3 years. Of the 19 trials, 11 reported statistically significant increases in BMD at one or more sites for the calcitriol group when compared to the placebo group [65, 67, 70, 71, 74, 75, 84, 87–90]. Five trials reported no difference in BMD changes between those receiving calcitriol therapy and those in the placebo group [72, 78, 82, 85, 91]. The final three trials found that calcitriol therapy was equivalent to proven bone therapies, such as bisphosphonates [76], high-dose vitamin D [83], and alfacalcidol (a calcitriol prodrug) [86].

The majority of the 19 studies examining monotherapy calcitriol in regard to BMD changes were conducted among postmenopausal women, many of whom had measurable bone loss [65, 67, 70, 72, 74, 83–87, 89, 90]. Of the 12 studies investigating calcitriol therapy in relation to BMD changes among postmenopausal women, eight reported that calcitriol had significant favorable effects when compared to placebo treatment [65, 67, 70, 74, 84, 87, 89, 90]. All studies compared the effects of calcitriol against a placebo arm, except one study that used historical controls [67] and another study that used a one-arm trial design [84]. Changes in BMD were commonly observed in the lumbar region, the most common site of osteoporotic fractures, and four studies reported significant differences at this site [65, 70, 87, 90]. Three studies detected significant changes in the distal radius [65, 84, 89], two studies in the hip region [70, 74], and two studies found a difference for total BMD [67, 87]. Changes in bone density were modest; many studies reported 1–3% annual increases in BMD, while participants in the control arms continued to lose BMD over the course of the study. Two trials reported no difference between calcitriol therapy and placebo. Falch et al. found no difference in bone mineral content between daily calcitriol (0.25 μg b.i.d.) and 400 IU of vitamin D [85], and Ott et al. reported no difference in lumbar BMD between calcitriol and placebo treatments over 2 years [72]. One study found that the increase in lumbar BMD for calcitriol therapy was equivalent to that produced by 100,000 IU of vitamin D per week [83], and another study concluded that the changes in lumbar BMD were equal for calcitriol therapy and alfacidiol (another vitamin D analog) therapy [86]. Overall, the majority of trials demonstrated that calcitriol can slow or even reverse bone loss among postmenopausal women, many of whom already have measurable bone loss.

Three of the 20 studies examining monotherapy calci-triol in relation to bone health did so among patients who underwent organ transplants [75, 76, 78]. Sambrook et al. found that transplant patients administered calcitriol (0.5–0.75 μg daily), and calcium had significantly greater increases in BMD than patients who received calcium alone [75]. Another study found no difference in BMD change between a group of transplant patients receiving calcitriol, calcium supplementation, and hormonal therapy compared to a group receiving only calcium and hormonal therapy [78]. The final study involving transplant patients found one group of patients receiving the bisphosphonate, alendronate, and another group receiving calcitriol lost significantly less BMD compared to patients in the control arm [76]. This study also found no difference in BMD change at the femur and hip between those receiving alendronate and calcitriol. Three studies administered calcitriol to patients who had experienced bone loss as a result of corticosteroid therapy [71, 88, 91]. Lambrinoudaki et al. [71] found significantly increased lumbar BMD, and Mirzaei et al. [88] found significantly increased femoral BMD for those in the calcitriol arm when compared to those in the control arm. Diaz et al. [91] administered calcitriol to 24 children aged two to 11 with

acute lymphoblastic leukemia. Overall, no significant change in lumbar BMD was found, but a significant increase in lumbar BMD was reported in the calcitriol arm for those with a low baseline BMD. The final study involving calcitriol monotherapy was conducted was among males with primary osteoporosis. This study reported a 2% increase in femoral BMD for the calcitriol group and no change for the placebo group, although the difference was not significant [82].

Ten studies reported the effect of calcitriol monotherapy on fracture incidence, although, the majority were post-hoc analyses and lacked statistical power [65, 67, 72, 75, 76, 82, 85, 92–94]. Two separate one-arm trials reported significantly lower fracture rates after calcitriol therapy compared to baseline fracture rates [67, 92]. One large trial reported a fracture rate of 12 per 100 patient-years (PY) for the calcitriol arm and a fracture rate of 44 per 100 PY for the control group ($P<0.05$) at 3 years of follow-up [94]. Another trial reported a fracture rate of 297 per 1,000 PY for those who were administered calcitriol compared to 823 per 1,000 PY given a placebo [93]. Among transplant patients, Sambrook et al. [75] reported 22 fractures in the control group versus one fracture in the calcitriol group ($P< 0.05$), and Shane et al. [76] found only 3.4% of those given calcitriol sustained a new fracture compared to 13.6% in the control group, although the difference was not statistically significant. The remaining four trials found no significant difference in fracture rates between the calcitriol and control groups [65, 72, 82, 85].

Although the results of these studies are mixed, the majority concluded monotherapy calcitriol is effective in preventing bone loss. Eleven [65, 67, 70, 71, 74, 75, 84, 87–90] of 19 studies found statistically significant increases in BMD for calcitriol when compared to control conditions and three [76, 83, 86] trials reported calcitriol was equivalent to other treatments that have been shown to prevent bone loss. Of the five studies [72, 78, 82, 85, 91] that reported null results, four [72, 82, 85, 91] had relatively small samples ($n<90$), and one trial administered vitamin D to the control group [85]. Five [67, 75, 92–94] of ten [65, 67, 72, 75, 76, 82, 85, 92–94] studies that reported fracture rates found calcitriol significantly reduced fractures. Three [65, 76, 82] other studies reported findings suggestive of a protective effect from calcitriol but lacked statistical significance, while the final two [72, 85] trials reported no difference in fracture rates. Seven trials reported increased hypercalcemia as a result of calcitriol therapy [65, 67, 72, 75, 76, 85, 89]. Calcitriol monotherapy may protect against bone loss, but the evidence is less convincing for fractures, which were studied as primary end-points in a minority of studies.

Combination calcitriol therapy and bone biomarkers

Studies have examined the effectiveness of calcitriol in combination with other effective bone therapeutics, such as bisphosphonates, HRT, corticosteroids, and calcitonin, through bone biomarkers among individuals with primary and secondary osteoporosis [53, 95–101]. Three studies used calcitriol in combination with HRT among postmenopausal women [53, 96, 99]. The first lasted only 5 days and found subjects assigned to calcitriol plus HRT experienced a significant drop in PTH compared to subjects given HRT alone [96]. No difference in bone resorption between the two groups was observed. The other two studies noted significant decreases in osteocalcin levels for the HRT/calcitriol combination group when compared to HRT alone [53, 99]. In one study, the combination of calcitriol and HRT significantly reduced bone resportion and PTH levels compared to the placebo group [53].

Two trials examined the combination of alendronate plus calcitriol on bone biomarkers among postmenopausal women with osteoporosis [95, 100]. Barone et al. found that secondary hyperparathyroidism decreased the beneficial effect of alendronate on BMD in osteoporotic women. The combination of alendronate and calcitriol increased the response

to alendronate due to a reduction in PTH levels by calcitriol [95]. Rhee et al. reported significant reductions in both bone resorption ($P<0.01$) and bone formation ($P< 0.05$) for the calcitriol/alendronate group compared to the control group that received alfacalcidiol [100]. Two other studies used calcitriol in combination with calcitonin; one study investigated changes among individuals with osteoporosis [97] and the other study used patients undergoing corticosteroid therapy [101]. Eriksson et al. [97] failed to find any difference in PTH levels between the groups, while Sambrook et al. [101] found osteocalcin levels were significantly reduced for individuals given either a combination of calcitriol, calcitonin, and calcium or a combination of calcitriol and calcium compared to the calcium only group. The final study reported the effects of corticosteroids, which diminish bone density and calcitriol among healthy male volunteers over the course of 28 days [98]. Males receiving corticosteroids had diminished bone formation, while males receiving only calcitriol had increased bone formation, and calcitriol appeared to attenuate the decrease in bone formation in those who received a combination of corticosteroids and calcitriol.

Of the seven studies that used calcitriol in combination with other therapeutic bone agents, six reported significant changes in at least one bone biomarker that favored the calcitriol combination arm [53, 95, 96, 98–101]. Four of the studies reported calcitriol had a synergistic effect in combination with the therapeutic agent that was used [53, 95, 99, 101]. Hypercalcemia was a reported side-effect of calcitriol therapy in four studies [53, 97, 99, 101]. Overall, calcitriol in combination with other bone agents was well-tolerated and had favorable effects on bone biomarkers across different populations (Table 2).

Combination calcitriol therapy, BMD, and fractures

Eleven studies evaluated the effect of calcitriol in combination with various therapeutic bone agents on BMD changes among a variety of populations [53, 95, 97, 99–106]. Study durations ranged from 6 months to 3 years, with the majority lasting between 1 and 2 years. All of the studies administered daily doses of 0.5 μg of calcitriol, except one study that used a mean dose of 0.6 μg of calcitriol [101] and another study that gave participants only 0.25 μg of calcitriol every other day [105]. Ten studies measured BMD changes in the lumbar region [53, 95, 97, 99–103, 105, 106], five studies used femoral BMD [53, 101, 102, 105, 106], four studies used radial BMD [97, 101, 102, 104], three studies used total body BMD [53, 99, 102], and two studies used hip BMD [95, 99]. All of the studies enrolled postmenopausal women with osteoporosis, except one study that enrolled participants with corticosteroid-induced osteoporosis [101] and another that enrolled healthy postmenopausal women [53]. Six studies used calcitriol in combination with bisphosphonates [95, 100, 102, 103, 105, 106], three studies used calcitriol and HRT [53, 99, 104], and three studies used calcitriol and calcitonin [97, 101, 103].

Of the six studies examining the combination of bisphosphonates plus calcitriol, all reported significant changes in BMD at one or more sites favoring the combination arm over the control arm [95, 100, 102, 103, 105, 106]. Four [95, 102, 105, 106] studies compared bisphosphonate monotherapy to combination bisphosphonate/calcitriol therapy, and three [95, 102, 106] of those studies found the combination to be more effective in increasing BMD than bisphosphonate monotherapy. Barone et al. reported a 3.7% increased in lumbar BMD for alendronate alone and a 6.8% increase in lumbar BMD for combination alendronate/calcitriol therapy after 1 year ($P<0.01$) [95]. Another study reported similar results: lumbar BMD increased by 2.7% for patients taking the bisphosphonate etidronate and 5.2% for those taking a combination of etidronate plus calcitriol ($P<0.05$) [106]. Frediani et al. found that calcium levels in urine were significantly increased by calcitriol and significantly decreased by alendronate, but calcium levels in urine in the combination group (calcitriol plus alendronate) remained stable compared to the baseline values. These findings may be

important in order to decrease the risk of hypercalcemia and for an inhibition of frequent episodes of hypercalciuria induced by calcitriol. Rhee et al. concluded the combination of calcitriol plus alendronate significantly increased lumbar BMD when compared to the vitamin D derivative alfacalcidiol [100]. The increase in BMD following combination therapy was greater than that following monotherapy calcitriol, with BMD increasing between 2–7% annually in the combination groups. These studies clearly show that the combination of bisphosphonates plus calcitriol is particularly effective at increasing BMD.

Three studies examined the effects of HRT in combination with calcitriol on postmenopausal women, and all three reported significant gains in BMD for the combination arm compared to the control arm [53, 99, 104]. In general, the increases in BMD were large, ranging between 2% and 4% annually. Two [53, 99] of the three studies concluded the combination of HRT plus calcitriol was significantly superior to HRT monotherapy in regard to BMD, while the third study [104] found no difference in BMD between HRT alone and the combination of HRT plus calcitriol. Of the two studies using a combination of calcitriol plus calcitonin, one [101] found significant increases in BMD for the combination group compared to the control group, while the other [97] did not find any difference between the two groups. Calcitriol in combination with HRT appears to be well tolerated and more efficacious than HRT alone, while the benefits of the combination of calcitriol plus calcitonin remain inconclusive.

Only two studies [53, 99] examined the effect of calcitriol in combination with HRT on fracture rates, and neither study was powered to detect a difference in fracture rates. Gallagher et al. reported a fracture rate of 4.9% for participants in the calcitriol only arm and 7.8% for participants in the combination HRT/calcitriol arm, compared to 10.7% and 11.9% for participants in the control arm and HRT only arm, respectively [53]. Nevertheless, these differences were not statistically significant. Gutteridge et al. found 12% of participants in the combination HRT/calcitriol arm suffered new fractures compared to 22% in the HRT alone arm, although the difference was not significant [99]. Preliminary evidence suggests calcitriol in combination with other therapeutic bone agents may reduce fracture rates, but more conclusive evidence from long-term studies is needed.

Results from the studies reviewed in this section show that calcitriol used in combination with other therapeutic bone agents significantly preserved BMD when compared to control treatment. Nine [53, 95, 99–102, 104–106] of the ten studies [53, 95, 97, 99–102, 104–106] reported significant changes in BMD that favored the calcitriol combination arm over the control arm. In addition, five [53, 95, 99, 102, 106] of seven [53, 95, 99, 102, 104–106] studies reported that calcitriol in combination with a therapeutic bone agent had a significantly greater effect on BMD compared to the therapeutic bone agent alone. Hypercalcemia was noted as a complication of calcitriol therapy in five studies [97, 99, 101, 103, 104, 106]. These results show that combination calcitriol therapy is more effective than monotherapy with calcitriol or other therapeutic bone agents with BMD gains between 2% and 7% annually for the combination arms. The large gains in BMD from combination therapy might be due to synergistic bone-preserving mechanisms, such as simultaneously decreasing bone resorption and increasing bone formation [107]. Future research is needed to determine the efficacy of combination calcitriol therapy on fracture rates among vulnerable populations (Table 3).

Limitations of calcitriol therapy, new dosing regimens, and future research

Many studies reported that calcitriol therapy was complicated by the occurrence of hypercalcemia and hypercalciuria among participants [53, 65, 72–76, 79, 83, 85, 87, 89, 97, 99, 101, 103, 104]. The occurrence of hypercalcemia was a common side effect (up to 40%) of calcitriol therapy and often triggered dose reductions or cessation of calcitriol therapy

altogether. The majority of studies that reported cases of hypercalcemia administered calcitriol more than once a day [75, 76, 79, 85, 89, 99, 101, 103, 104]. Evidence from these studies shows that frequency of dosing, as opposed to size of dose, was most closely related to the development of hypercalcemia. The failure of many physicians to use calcitriol therapy for bone loss may relate to fear of possible hypercalcemia. Despite the high incidence of hypercalcemia observed in these studies, the grade of toxicity was often described as mild or moderate (≤ grade 2 toxicity). No deaths or life-threatening toxicities were reported in any of the studies reviewed.

Recent research on the use of calcitriol as an antineo-plastic agent in the treatment of prostate cancer [108–115] found that hypercalcemia developed in most patients during daily calcitriol administration of slightly greater than standard replacement doses [116]. The introduction of intermittent dosing (three consecutive days a week or weekly dosing) using substantially higher doses significantly reduced the incidence of hypercalcemia. To date, more than 600 cancer patients have been enrolled in trials that administered high-dose intermittent calcitriol (≥30 μg/week calcitriol) [110, 112, 114, 115, 117–123]. The studies reported a low incidence of mild hypercalcemia (≤ grade 2), and there were no reports of deaths or severe hypercalcemia (≥grade 3) employing intermittent dosing despite using calcitriol amounts that far exceed standard replacement doses.

Clearly, there is scientific evidence from clinical trials for the use of calcitriol, both as a monotherapy or in combination with other therapeutic bone agents, in the prevention and treatment of bone loss. Despite this, calcitriol therapy has been hampered by the common occurrence of hypercalcemia, and a great deal of research is still needed. In addition, osteoporosis rates will increase due to population aging and the increased use of pharmacologic therapies that produce bone loss (hormone ablation therapy, corticosteroid therapy, etc.). The use of intermittent calcitriol therapy now provides new research opportunities involving bone health. Future research on calcitriol therapy should focus on discerning: (a) the effect of intermittent calcitriol therapy on bone mineral density and fracture risk; (b) the effect of intermittent calcitriol therapy on bone metabolism using the most sensitive and specific bone biomarkers (e.g., NTx, BSAP, Osteocalcin, and CTx); (c) the effect of intermittent calcitriol therapy for populations at high risk for secondary osteoporosis (e.g., hormonally sensitive cancers, corticosteroid therapy); (d) what the negative side effects of intermittent calcitriol therapy are and at what doses and time points they occur (e.g., hypercalcemia, renal complications, etc.); (e) what the optimal dose and frequency for intermittent calcitriol therapy in each specific population (e.g., post-menopausal women, hormonally sensitive breast or prostate cancer patients, organ transplant patients, etc.); (f) the effect and synergy of intermittent calcitriol therapy in combination with behavioral bone interventions such as weight-bearing exercise and resistance training on bone mineral density and fracture risk; (g) the effect and synergy of intermittent calcitriol therapy in combination with pharmacologic bone interventions such as new generation bisphosphonates; and (h) which combination of interventions provides the most effective means of preventing and treating bone loss. Future trials using intermittent calcitriol therapy for the treatment and prevention of bone loss should follow the Consolidated Standards of Reporting Trials guidelines [124]. Experimental designs should include validated measures of bone health (e.g., bone mineral density by DXA, clinical fractures, etc.) as primary study outcomes, adverse events should be carefully recorded and reported, and statistical analyses should use intent-to-treat analyses.

Conclusions

In conclusion, evidence suggests that calcitriol, alone and in combination with other therapeutic bone agents, may reduce or even reverse BMD loss among vulnerable

populations. Calcitriol used in combination with bisphosphonates and HRT was well tolerated. One common side-effect of calcitriol therapy was hypercalcemia, which usually presented as mild or moderate. Recent research shows that hypercalcemia rates can be reduced by using intermittent dosing regimen. Due to the success of intermittent dosing at reducing hypercalcemia rates, there are a number of new research opportunities involving calcitriol and bone health. Future trials of calcitriol should examine its effect in other populations at high risk for bone loss, such as those treated for hormonally responsive cancers and in combination with newer-generation bisphosphonates.

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References

1. United States. Public Health Service. Office of the Surgeon General. Bone health and osteoporosis a report of the Surgeon General. U.S. Dept. of Health and Human Services, Public Health Service; Rockville, MD, Washington, D.C: 2004.
2. Liu H, Paige NM, Goldzweig CL, Wong E, Zhou A, Suttorp MJ, Munjas B, Orwoll E, Shekelle P. Screening for osteoporosis in men: a systematic review for an American College of Physicians guideline. Ann Intern Med. 2008; 148:685–701. [PubMed: 18458282]
3. Looker AC, Bauer DC, Chesnut CH 3rd, Gundberg CM, Hochberg MC, Klee G, Kleerekoper M, Watts NB, Bell NH. Clinical use of biochemical markers of bone remodeling: current status and future directions. Osteoporos Int. 2000; 11:467–480. [PubMed: 10982161]
4. Miller PD, Baran DT, Bilezikian JP, Greenspan SL, Lindsay R, Riggs BL, Watts NB. Practical clinical application of biochemical markers of bone turnover: consensus of an expert panel. J Clin Densitom. 1999; 2:323–342. [PubMed: 10548827]
5. Garnero P, Delmas PD. Assessment of the serum levels of bone alkaline phosphatase with a new immunoradiometric assay in patients with metabolic bone disease. J Clin Endocrinol Metab. 1993; 77:1046–1053. [PubMed: 8104954]
6. Seeman E. Invited review: pathogenesis of osteoporosis. J Appl Physiol. 2003; 95:2142–2151. [PubMed: 14555675]
7. Dennison E, Mohamed MA, Cooper C. Epidemiology of osteoporosis. Rheum Dis Clin North Am. 2006; 32:617–629. [PubMed: 17288968]
8. Riggs BL, Khosla S, Melton LJ 3rd. Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev. 2002; 23:279–302. [PubMed: 12050121]
9. Stein E, Shane E. Secondary osteoporosis. Endocrinol Metab Clin North Am. 2003; 32:115–134. vii. [PubMed: 12699295]
10. Saag KG. Glucocorticoid-induced osteoporosis. Endocrinol Metab Clin North Am. 2003; 32:135–157. vii. [PubMed: 12699296]
11. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int. 2002; 13:777–787. [PubMed: 12378366]
12. Riggs BL, Khosla S, Melton LJ 3rd. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. J Bone Miner Res. 1998; 13:763–773. [PubMed: 9610739]
13. Cancer survivorship—United States, 1971–2001. MMWR Morb Mortal Wkly Rep. 2004; 53:526–529. [PubMed: 15215740]
14. Demark-Wahnefried W, Aziz NM, Rowland JH, Pinto BM. Riding the crest of the teachable moment: promoting long-term health after the diagnosis of cancer. J Clin Oncol. 2005; 23:5814–5830. [PubMed: 16043830]
15. Ganz PA. A teachable moment for oncologists: cancer survivors, 10 million strong and growing! J Clin Oncol. 2005; 23:5458–5460. [PubMed: 16043826]

16. Greep NC, Giuliano AE, Hansen NM, Taketani T, Wang HJ, Singer FR. The effects of adjuvant chemotherapy on bone density in postmenopausal women with early breast cancer. Am J Med. 2003; 114:653–659. [PubMed: 12798453]

17. Pfeilschifter J, Diel IJ. Osteoporosis due to cancer treatment: pathogenesis and management. J Clin Oncol. 2000; 18:1570–1593. [PubMed: 10735906]

18. Mittan D, Lee S, Miller E, Perez RC, Basler JW, Bruder JM. Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. J Clin Endocrinol Metab. 2002; 87:3656–3661. [PubMed: 12161491]

19. Shapiro CL, Manola J, Leboff M. Ovarian failure after adjuvant chemotherapy is associated with rapid bone loss in women with early-stage breast cancer. J Clin Oncol. 2001; 19:3306–3311. [PubMed: 11454877]

20. Jemal A, Ward E, Thun MJ. Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. Breast Cancer Res. 2007; 9:R28. [PubMed: 17477859]

21. Roach M 3rd. Current status of androgen suppression and radiotherapy for patients with prostate cancer. J Steroid Biochem Mol Biol. 1999; 69:239–245. [PubMed: 10418997]

22. Berruti A, Dogliotti L, Terrone C, Cerutti S, Isaia G, Tarabuzzi R, Reimondo G, Mari M, Ardissone P, De Luca S, Fasolis G, Fontana D, Rossetti SR, Angeli A. Changes in bone mineral density, lean body mass and fat content as measured by dual energy X-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. J Urol. 2002; 167:2361–2367. discussion 2367. [PubMed: 11992038]

23. Coleman RE, Banks LM, Girgis SI, Kilburn LS, Vrdoljak E, Fox J, Cawthorn SJ, Patel A, Snowdon CF, Hall E, Bliss JM, Coombes RC. Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. Lancet Oncol. 2007; 8:119–127. [PubMed: 17267326]

24. Oefelein MG, Ricchuiti V, Conrad W, Seftel A, Bodner D, Goldman H, Resnick M. Skeletal fracture associated with androgen suppression induced osteoporosis: the clinical incidence and risk factors for patients with prostate cancer. J Urol. 2001; 166:1724–1728. [PubMed: 11586210]

25. Andersen SJ. Osteoporosis in the older woman. Clin Obstet Gynecol. 2007; 50:752–766. [PubMed: 17762423]

26. Gass M, Dawson-Hughes B. Preventing osteoporosis-related fractures: an overview. Am J Med. 2006; 119:S3–S11. [PubMed: 16563939]

27. Riggs BL, Melton LJ 3rd. The worldwide problem of osteoporosis: insights afforded by epidemiology. Bone. 1995; 17:505S–511S. [PubMed: 8573428]

28. Ray NF, Chan JK, Thamer M, Melton LJ 3rd. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. J Bone Miner Res. 1997; 12:24–35. [PubMed: 9240722]

29. Richmond J, Aharonoff GB, Zuckerman JD, Koval KJ. Mortality risk after hip fracture. J Orthop Trauma. 2003; 17:53–56. [PubMed: 12499968]

30. Melton LJ 3rd. Adverse outcomes of osteoporotic fractures in the general population. J Bone Miner Res. 2003; 18:1139–1141. [PubMed: 12817771]

31. Chrischilles EA, Butler CD, Davis CS, Wallace RB. A model of lifetime osteoporosis impact. Arch Intern Med. 1991; 151:2026–2032. [PubMed: 1929691]

32. Orwoll, ES. Osteoporosis in men: the effects of gender on skeletal health. Academic; San Diego: 1999.

33. United States. Congress. Office of Technology Assessment. Hip fracture outcomes in people age fifty and over. U.S. G.P.O; Washington, D.C, The Office: 1994.

34. Ross PD. Clinical consequences of vertebral fractures. Am J Med. 1997; 103:30S–42S. discussion 42 S–43 S. [PubMed: 9302895]

35. Magaziner J, Hawkes W, Hebel JR, Zimmerman SI, Fox KM, Dolan M, Felsenthal G, Kenzora J. Recovery from hip fracture in eight areas of function. J Gerontol. 2000; 55:M498–M507.

36. Tosteson AN, Hammond CS. Quality-of-life assessment in osteoporosis: health-status and preference-based measures. PharmacoEcon. 2002; 20:289–303.

37. Papaioannou A, Watts NB, Kendler DL, Yuen CK, Adachi JD, Ferko N. Diagnosis and management of vertebral fractures in elderly adults. Am J Med. 2002; 113:220–228. [PubMed: 12208381]
38. O'Donnell S, Moher D, Thomas K, Hanley DA, Cranney A. Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls. J Bone Miner Metab. 2008; 26:531–542. [PubMed: 18979152]
39. Lau KH, Baylink DJ. Vitamin D therapy of osteoporosis: plain vitamin D therapy versus active vitamin D analog (D-hormone) therapy. Calcif Tissue Int. 1999; 65:295–306. [PubMed: 10485982]
40. Frolik CA, Deluca HF. 1, 25-dihydroxycholecalciferol: the metabolite of vitamin D responsible for increased intestinal calcium transport. Arch Biochem Biophys. 1971; 147:143–147. [PubMed: 4329860]
41. Shiraishi A, Higashi S, Ohkawa H, Kubodera N, Hirasawa T, Ezawa I, Ikeda K, Ogata E. The advantage of alfacalcidol over vitamin D in the treatment of osteoporosis. Calcif Tissue Int. 1999; 65:311–316. [PubMed: 10485984]
42. Richy F, Ethgen O, Bruyere O, Reginster JY. Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: a meta-analysis of their effects on bone mineral density and fracture rate. Osteoporos Int. 2004; 15:301–310. [PubMed: 14740153]
43. Bischoff HA, Stahelin HB, Tyndall A, Theiler R. Relationship between muscle strength and vitamin D metabolites: are there therapeutic possibilities in the elderly? Z Rheumatol. 2000; 59(Suppl 1):39–41. [PubMed: 10769434]
44. Bischoff HA, Stahelin HB, Urscheler N, Ehrsam R, Vonthein R, Perrig-Chiello P, Tyndall A, Theiler R. Muscle strength in the elderly: its relation to vitamin D metabolites. Arch Phys Med Rehabil. 1999; 80:54–58. [PubMed: 9915372]
45. Xia WB, Zhang ZL, Wang HF, Meng XW, Zhang Y, Zhu GY, Xing XP, Liu JL, Wang LH, Jiang Y, Weng SF, Xu T, Hu YY, Yu W, Tian JP. The efficacy and safety of calcitriol and/or Caltrate D in elderly Chinese women with low bone mass. Acta Pharmacol Sin. 2009; 30:372–378. [PubMed: 19262561]
46. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med. 1988; 319:1701–1707. [PubMed: 3205267]
47. Evans JG. Falls and fractures. Age Ageing. 1988; 17:361–364. [PubMed: 3239498]
48. Dukas L, Staehelin HB, Schacht E, Bischoff HA. Better functional mobility in community-dwelling elderly is related to D-hormone serum levels and to daily calcium intake. J Nutr Health Aging. 2005; 9:347–351. [PubMed: 16222401]
49. Faulkner KA, Cauley JA, Zmuda JM, Landsittel DP, Newman AB, Studenski SA, Redfern MS, Ensrud KE, Fink HA, Lane NE, Nevitt MC. Higher 1,25-dihydroxyvitamin D3 concentrations associated with lower fall rates in older community-dwelling women. Osteoporos Int. 2006; 17:1318–1328. [PubMed: 16788853]
50. Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2004; 52:1121–1129. [PubMed: 15209650]
51. Muir SW, Berg K, Chesworth B, Klar N, Speechley M. Quantifying the magnitude of risk for balance impairment on falls in community-dwelling older adults: a systematic review and meta-analysis. J Clin Epidemiol. 200910.1016/j.jclinepi.2009. 06.010
52. Gallagher JC. The effects of calcitriol on falls and fractures and physical performance tests. J Steroid Biochem Mol Biol. 2004; 89–90:497–501.
53. Gallagher JC, Fowler SE, Detter JR, Sherman SS. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. J Clin Endocrinol Metab. 2001; 86:3618–3628. [PubMed: 11502787]
54. Richy F, Dukas L, Schacht E. Differential effects of d-hormone analogs and native vitamin d on the risk of falls: a comparative meta-analysis. Calcif Tissue Int. 2008; 82:102–107. [PubMed: 18239843]

55. Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database SystRev. 2005:CD000227.
56. Richy F, Schacht E, Bruyere O, Ethgen O, Gourlay M, Reginster JY. Vitamin D analogs versus native vitamin D in preventing bone loss and osteoporosis-related fractures: a comparative meta-analysis. Calcif Tissue Int. 2005; 76:176–186. [PubMed: 15692726]
57. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev. 2009; 2:CD000227. [PubMed: 19370554]
58. Jones G, Hogan DB, Yendt E, Hanley DA. Prevention and management of osteoporosis: consensus statements from the Scientific Advisory Board of the Osteoporosis Society of Canada. 8. Vitamin D metabolites and analogs in the treatment of osteoporosis. CMAJ. 1996; 155:955–961. [PubMed: 8837546]
59. Nuti R, Bonucci E, Brancaccio D, Gallagher JC, Gennari C, Mazzuoli G, Passeri M, Sambrook P. The role of calcitriol in the treatment of osteoporosis. Calcif Tissue Int. 2000; 66:239–240. [PubMed: 10666502]
60. de Nijs RN, Jacobs JW, Algra A, Lems WF, Bijlsma JW. Prevention and treatment of glucocorticoid-induced osteoporosis with active vitamin D3 analogues: a review with meta-analysis of randomized controlled trials including organ transplantation studies. Osteoporos Int. 2004; 15:589–602. [PubMed: 15138667]
61. Dechant KL, Goa KL. Calcitriol. A review of its use in the treatment of postmenopausal osteoporosis and its potential in corticosteroid-induced osteoporosis. Drugs Aging. 1994; 5:300–317. [PubMed: 7827399]
62. Eastell R, Hannon RA. Biomarkers of bone health and osteoporosis risk. Proc Nutr Soc. 2008; 67:157–162. [PubMed: 18412989]
63. Garnero P. Biomarkers for osteoporosis management: utility in diagnosis, fracture risk prediction and therapy monitoring. Mol Diagn Ther. 2008; 12:157–170. [PubMed: 18510379]
64. Pagani F, Francucci CM, Moro L. Markers of bone turnover: biochemical and clinical perspectives. J Endocrinol Invest. 2005; 28:8–13. [PubMed: 16550716]
65. Aloia JF, Vaswani A, Yeh JK, Ellis K, Yasumura S, Cohn SH. Calcitriol in the treatment of postmenopausal osteoporosis. Am J Med. 1988; 84:401–408. [PubMed: 3279769]
66. Caniggia A, Nuti R, Galli M, Lore F, Turchetti V, Righi GA. Effect of a long-term treatment with 1, 25-dihydroxyvitamin D3 on osteocalcin in postmenopausal osteoporosis. Calcif Tissue Int. 1986; 38:328–332. [PubMed: 3089554]
67. Caniggia A, Nuti R, Lore F, Martini G, Turchetti V, Righi G. Long-term treatment with calcitriol in postmenopausal osteoporosis. Metabolism. 1990; 39:43–49. [PubMed: 2325571]
68. Gallagher JC, Jerpbak CM, Jee WS, Johnson KA, DeLuca HF, Riggs BL. 1, 25-Dihydroxyvitamin D3: short- and long-term effects on bone and calcium metabolism in patients with postmenopausal osteoporosis. Proc Natl Acad Sci U S A. 1982; 79:3325–3329. [PubMed: 6954482]
69. Gram J, Junker P, Nielsen HK, Bollerslev J. Dose-response effect of short-term calcitriol treatment on bone and mineral metabolism in normal males. Bone. 1996; 18:539–544. [PubMed: 8805994]
70. Inanir A, Ozoran K, Tutkak H, Mermerci B. The effects of calcitriol therapy on serum interleukin-1, interleukin-6 and tumour necrosis factor-alpha concentrations in post-menopausal patients with osteoporosis. J Int Med Res. 2004; 32:570–582. [PubMed: 15587751]
71. Lambrinoudaki I, Chan DT, Lau CS, Wong RW, Yeung SS, Kung AW. Effect of calcitriol on bone mineral density in premenopausal Chinese women taking chronic steroid therapy. A randomized, double blind, placebo controlled study. J Rheumatol. 2000; 27:1759–1765. [PubMed: 10914864]
72. Ott SM, Chesnut CH 3rd. Calcitriol treatment is not effective in postmenopausal osteoporosis. Ann Intern Med. 1989; 110:267–274. [PubMed: 2913914]
73. Riggs BL, Nelson KI. Effect of long term treatment with calcitriol on calcium absorption and mineral metabolism in postmenopausal osteoporosis. J Clin Endocrinol Metab. 1985; 61:457–461. [PubMed: 3926808]
74. Sairanen S, Karkkainen M, Tahtela R, Laitinen K, Makela P, Lamberg-Allardt C, Valimaki MJ. Bone mass and markers of bone and calcium metabolism in postmenopausal women treated with

1,25-dihydroxyvitamin D (Calcitriol) for four years. Calcif Tissue Int. 2000; 67:122–127. [PubMed: 10920216]

75. Sambrook P, Henderson NK, Keogh A, MacDonald P, Glanville A, Spratt P, Bergin P, Ebeling P, Eisman J. Effect of calcitriol on bone loss after cardiac or lung transplantation. J Bone Miner Res. 2000; 15:1818–1824. [PubMed: 10977001]
76. Shane E, Addesso V, Namerow PB, McMahon DJ, Lo SH, Staron RB, Zucker M, Pardi S, Maybaum S, Mancini D. Alendronate versus calcitriol for the prevention of bone loss after cardiac transplantation. N Engl J Med. 2004; 350:767–776. [PubMed: 14973216]
77. Sirtori P, Sosio C, Resmini G, Rubinacci A. Effect of short course of 1,25-dihydroxyvitamin D3 on biochemical markers of bone remodelling in postmenopausal women. Pharmacol Res. 1996; 33:353–359. [PubMed: 8971958]
78. Stempfle HU, Werner C, Echtler S, Wehr U, Rambeck WA, Siebert U, Uberfuhr P, Angermann CE, Theisen K, Gartner R. Prevention of osteoporosis after cardiac transplantation: a prospective, longitudinal, randomized, double-blind trial with calcitriol. Transplantation. 1999; 68:523–530. [PubMed: 10480411]
79. Tjellesen L, Christiansen C, Rodbro P. Effect of 1,25-dihydroxyvitamin D3 on biochemical indices of bone turnover in postmenopausal women. Acta Med Scand. 1984; 215:411–415. [PubMed: 6547563]
80. Tsukamoto Y, Watanabe T, Nakagami T, Morishita K. Effect of treatment with oral calcitriol on calcium metabolism and fasting serum 25(OH)- or 1,25(OH)2-vitamin D level in Japanese postmenopausal women. Endocr J. 2003; 50:681–687. [PubMed: 14709838]
81. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996; 312:1254–1259. [PubMed: 8634613]
82. Ebeling PR, Wark JD, Yeung S, Poon C, Salehi N, Nicholson GC, Kotowicz MA. Effects of calcitriol or calcium on bone mineral density, bone turnover, and fractures in men with primary osteoporosis: a two-year randomized, double blind, double placebo study. J Clin Endocrinol Metab. 2001; 86:4098–4103. [PubMed: 11549632]
83. Arthur RS, Piraino B, Candib D, Cooperstein L, Chen T, West C, Puschett J. Effect of low-dose calcitriol and calcium therapy on bone histomorphometry and urinary calcium excretion in osteopenic women. Miner Electrolyte Metab. 1990; 16:385–390. [PubMed: 2089252]
84. Dambacher MA, Kranich M, Schacht E, Neff M. Can the fast bone loss in osteoporotic and osteopenic patients be stopped with active vitamin D metabolites? Calcif Tissue Int. 1997; 60:115–118. [PubMed: 9030492]
85. Falch JA, Odegaard OR, Finnanger AM, Matheson I. Postmenopausal osteoporosis: no effect of three years treatment with 1,25-dihydroxycholecalciferol. Acta Med Scand. 1987; 221:199–204. [PubMed: 3035879]
86. Fujita T. Studies of osteoporosis in Japan. Metabolism. 1990; 39:39–42. [PubMed: 2325570]
87. Gallagher JC, Goldgar D. Treatment of postmenopausal osteoporosis with high doses of synthetic calcitriol. A randomized controlled study. Ann Intern Med. 1990; 113:649–655. [PubMed: 2221645]
88. Mirzaei S, Zajicek HK, Knoll P, Hahn M, Levi M, Kohn H, Pohl W. Effect of rocaltrol on bone mass in patients with pulmonary disease treated with corticosteroids. J Asthma. 2003; 40:251–255. [PubMed: 12807168]
89. Need AG, Nordin C, Horowitz M, Morris HA. Calcium and calcitriol therapy in osteoporotic postmenopausal women with impaired calcium absorption. Metabolism. 1990; 39:53–54. [PubMed: 2325573]
90. Tilyard M. Low-dose calcitriol versus calcium in established postmenopausal osteoporosis. Metabolism. 1990; 39:50–52. [PubMed: 2325572]
91. Diaz PR, Neira LC, Fischer SG, Teresa Torres MC, Milinarsky AT, Giadrosich VR, Arriagada MM, Arinoviche RS, Casanova DM. Effect of 1,25(OH)2-vitamin D on bone mass in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2008; 30:15–19. [PubMed: 18176174]

92. Caniggia A, Nuti R, Martini G, Frediani B, Giovani S, Valenti R, Silvestri G, Matarazzo M. Efficacy and safety of long-term, open-label treatment with calcitriol in postmenopausal osteoporosis: a retrospective analysis. Curr Ther Res. 1996; 57:857–868.

93. Gallagher JC, Riggs BL, Recker RR, Goldgar D. The effect of calcitriol on patients with postmenopausal osteoporosis with special reference to fracture frequency. Proc Soc Exp Biol Med. 1989; 191:287–292. [PubMed: 2740360]

94. Tilyard MW, Spears GF, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. N Engl J Med. 1992; 326:357–362. [PubMed: 1729617]

95. Barone A, Giusti A, Pioli G, Girasole G, Razzano M, Pizzonia M, Palummeri E, Bianchi G. Secondary hyperparathyroidism due to hypovitaminosis D affects bone mineral density response to alendronate in elderly women with osteoporosis: a randomized controlled trial. J Am Geriatr Soc. 2007; 55:752–757. [PubMed: 17493196]

96. Cosman F, Nieves J, Shen V, Lindsay R. Oral 1,25-dihydroxyvitamin D administration in osteoporotic women: effects of estrogen therapy. J Bone Miner Res. 1995; 10:594–600. [PubMed: 7610930]

97. Eriksson SA, Lindgren JU. Combined treatment with calcitonin and 1,25-dihydroxyvitamin D3 for osteoporosis in women. Calcif Tissue Int. 1993; 53:26–28. [PubMed: 8348381]

98. Gram J, Junker P, Nielsen HK, Bollerslev J. Effects of short-term treatment with prednisolone and calcitriol on bone and mineral metabolism in normal men. Bone. 1998; 23:297–302. [PubMed: 9737353]

99. Gutteridge DH, Holzherr ML, Retallack RW, Price RI, Will RK, Dhaliwal SS, Faulkner DL, Stewart GO, Stuckey BG, Prince RL, Criddle RA, Drury PJ, Tran L, Bhagat CI, Kent GN, Jamrozik K. A randomized trial comparing hormone replacement therapy (HRT) and HRT plus calcitriol in the treatment of postmenopausal osteoporosis with vertebral fractures: benefit of the combination on total body and hip density. Calcif Tissue Int. 2003; 73:33–43. [PubMed: 14506952]

100. Rhee Y, Kang M, Min Y, Byun D, Chung Y, Ahn C, Baek K, Mok J, Kim D, Kim D, Kim H, Kim Y, Myoung S, Kim D, Lim SK. Effects of a combined alendronate and calcitriol agent (Maxmarvil) on bone metabolism in Korean postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. Osteoporos Int. 2006; 17:1801–1807. [PubMed: 17019520]

101. Sambrook P, Birmingham J, Kelly P, Kempler S, Nguyen T, Pocock N, Eisman J. Prevention of corticosteroid osteoporosis. A comparison of calcium, calcitriol, and calcitonin. N Engl J Med. 1993; 328:1747–1752. [PubMed: 7684512]

102. Frediani B, Allegri A, Bisogno S, Marcolongo R. Effects of combined treatment with calcitriol plus alendronate on bone mass and bone turnover in postmenopausal osteoporosis: two years of continuous treatment. Clinical Drug Investigation. 1998; 15:235.

103. Gurlek A, Bayraktar M, Gedik O. Comparison of calcitriol treatment with etidronate-calcitriol and calcitonin-calcitriol combinations in Turkish women with postmenopausal osteoporosis: a prospective study. Calcif Tissue Int. 1997; 61:39–43. [PubMed: 9192511]

104. Jensen GF, Christiansen C, Transbol I. Treatment of post menopausal osteoporosis. A controlled therapeutic trial comparing oestrogen/gestagen, 1,25-dihydroxy-vitamin D3 and calcium. Clin Endocrinol (Oxf). 1982; 16:515–524. [PubMed: 7044620]

105. Malavolta N, Zanardi M, Veronesi M, Ripamonti C, Gnudi S. Calcitriol and alendronate combination treatment in menopausal women with low bone mass. Int J Tissue React. 1999; 21:51–59. [PubMed: 10568224]

106. Masud T, Mulcahy B, Thompson AV, Donnelly S, Keen RW, Doyle DV, Spector TD. Effects of cyclical etidronate combined with calcitriol versus cyclical etidronate alone on spine and femoral neck bone mineral density in postmenopausal osteoporotic women. Ann Rheum Dis. 1998; 57:346–349. [PubMed: 9771208]

107. Schacht E, Dukas L, Richy F. Combined therapies in osteoporosis: bisphosphonates and vitamin D-hormone analogs. JMNI. 2007; 7:174–184. [PubMed: 17627088]

108. Chan JS, Beer TM, Quinn DI, Pinski JK, Garzotto M, Sokoloff M, Dehaze DR, Ryan CW. A phase II study of high-dose calcitriol combined with mitoxantrone and prednisone for androgen-independent prostate cancer. BJU Int. 2008; 102:1601–1606. [PubMed: 18782306]

109. Beer TM, Ryan CW, Venner PM, Petrylak DP, Chatta GS, Ruether JD, Redfern CH, Fehrenbacher L, Saleh MN, Water-house DM, Carducci MA, Vicario D, Dreicer R, Higano CS, Ahmann FR, Chi KN, Henner WD, Arroyo A, Clow FW. Double-blinded randomized study of high-dose calcitriol plus docetaxel compared with placebo plus docetaxel in androgen-independent prostate cancer: a report from the ASCENT Investigators. J Clin Oncol. 2007; 25:669–674. [PubMed: 17308271]

110. Beer TM, Eilers KM, Garzotto M, Egorin MJ, Lowe BA, Henner WD. Weekly high-dose calcitriol and docetaxel in metastatic androgen-independent prostate cancer. J Clin Oncol. 2003; 21:123–128. [PubMed: 12506180]

111. Petrioli R, Pascucci A, Francini E, Marsili S, Sciandivasci A, De Rubertis G, Barbanti G, Manganelli A, Salvestrini F, Francini G. Weekly high-dose calcitriol and docetaxel in patients with metastatic hormone-refractory prostate cancer previously exposed to docetaxel. BJU Int. 2007; 100:775–779. [PubMed: 17535276]

112. Tiffany NM, Ryan CW, Garzotto M, Wersinger EM, Beer TM. High dose pulse calcitriol, docetaxel and estramustine for androgen independent prostate cancer: a phase I/II study. J Urol. 2005; 174:888–892. [PubMed: 16093981]

113. Fakih MG, Trump DL, Muindi JR, Black JD, Bernardi RJ, Creaven PJ, Schwartz J, Brattain MG, Hutson A, French R, Johnson CS. A phase I pharmacokinetic and pharmaco-dynamic study of intravenous calcitriol in combination with oral gefitinib in patients with advanced solid tumors. Clin Cancer Res. 2007; 13:1216–1223. [PubMed: 17317832]

114. Beer TM, Javle MM, Ryan CW, Garzotto M, Lam GN, Wong A, Henner WD, Johnson CS, Trump DL. Phase I study of weekly DN-101, a new formulation of calcitriol, in patients with cancer. Cancer Chemother Pharmacol. 2007; 59:581–587. [PubMed: 17066293]

115. Trump DL, Potter DM, Muindi J, Brufsky A, Johnson CS. Phase II trial of high-dose, intermittent calcitriol (1,25 dihydroxyvitamin D3) and dexamethasone in androgen-independent prostate cancer. Cancer. 2006; 106:2136–2142. [PubMed: 16598750]

116. Beer TM. ASCENT: the androgen-independent prostate cancer study of calcitriol enhancing taxotere. BJU Int. 2005; 96:508–513. [PubMed: 16104901]

117. Beer TM, Garzotto M, Katovic NM. High-dose calcitriol and carboplatin in metastatic androgen-independent prostate cancer. Am J Clin Oncol. 2004; 27:535–541. [PubMed: 15596926]

118. Beer TM, Javle M, Lam GN, Henner WD, Wong A, Trump DL. Pharmacokinetics and tolerability of a single dose of DN-101, a new formulation of calcitriol, in patients with cancer. Clin Cancer Res. 2005; 11:7794–7799. [PubMed: 16278401]

119. Beer TM, Munar M, Henner WD. A Phase I trial of pulse calcitriol in patients with refractory malignancies: pulse dosing permits substantial dose escalation. Cancer. 2001; 91:2431–2439. [PubMed: 11413535]

120. Beer TM, Myrthue A, Garzotto M, O'Hara MF, Chin R, Lowe BA, Montalto MA, Corless CL, Henner WD. Randomized study of high-dose pulse calcitriol or placebo prior to radical prostatectomy. Cancer Epidemiol Biomarkers Prev. 2004; 13:2225–2232. [PubMed: 15598784]

121. Beer TM, Ryan CW, Venner PM, Petrylak DP, Chatta GS, Ruether JD, Chi KN, Young J, Henner WD. Intermittent chemotherapy in patients with metastatic androgen-independent prostate cancer: results from ASCENT, a double-blinded, randomized comparison of high-dose calcitriol plus docetaxel with placebo plus docetaxel. Cancer. 2008; 112:326–330. [PubMed: 17960793]

122. Muindi JR, Peng Y, Potter DM, Hershberger PA, Tauch JS, Capozzoli MJ, Egorin MJ, Johnson CS, Trump DL. Pharmacokinetics of high-dose oral calcitriol: results from a phase 1 trial of calcitriol and paclitaxel. Clin Pharmacol Ther. 2002; 72:648–659. [PubMed: 12496746]

123. Muindi JR, Potter DM, Peng Y, Johnson CS, Trump DL. Pharmacokinetics of liquid calcitriol formulation in advanced solid tumor patients: comparison with caplet formulation. Cancer Chemother Pharmacol. 2005; 56:492–496. [PubMed: 15918041]

124. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001; 357:1191–1194. [PubMed: 11323066]

Table 1

Detailed search strategy and number of articles

1 calcitriol	*n*=14,436
2 1,25 dihydroxyvitamin D	*n*=3,601
3 1,25 dihydroxycholecalciferol	*n*=14,918
4 Rocaltrol	*n*=14,443
5 Vitamin D analog	*n*=724
6 Vitamin D hormone	*n*=14,652
7 or/1–7	*n*=24,568
8 Bone loss	*n*=84,695
9 Bone mineral density	*n*=46,613
10 Bone health	*n*=39,081
11 Bone remodeling	*n*=41,701
12 Bone turnover	*n*=160,239
13 Fractures	*n*=141,731
14 or/8–13	*n*=390,570
15 7 and 14	*n*=10,744
16 Limit English/15	*n*=9,131
17 Limit Clinical Trial or Randomized Controlled Trial/16	*n*=893

Table 2

Study characteristics of trials involving calcitriol and bone biomarkers

Trial	Year	Number of participants	Study population	Trial duration	Treatments	Results
Gram et al. [69]	1996	36	Healthy males	1 week	A) 2.0 μg/day Calci	PTH: A,B<C
					B) 1.0 μg/day Calci	BSAP: A,B<C
					C) Placebo	PICP: A,B>C
						CTx: NS
Sirtori et al. [77]	1996	12	Postmenopausal osteopenic women	1 week	A) 1.0 μg/day Calci	PTH: Post A<Pre A
					B) 0.5 μg/day Calci	PTH: Post B<Pre B
						Osteo: Post A>Pre A
						Osteo: Post B/Pre B, NS
						BSAP: Post A/Pre A, NS
						BSAP: Post B/Pre B, NS
Tsukamoto et al. [80]	2003	18	Postmenopausal women	4 weeks	A) 0.5 μg/day Calci	NTX: A<B
					B) Control	PTH: A<B
						BSAP: NS
Aloia et al. [65]	1988	27	Postmenopausal osteoporotic women	2 years	A) 0.8 μg/day Calci+800 mg calcium	PTH: NS
					B) 400 IU/day Vit D+800 mg calcium	
Caniggia et al. [66]	1986	25	Postmenopausal osteoporotic women	6–30 months	A) 1.0 μg/day Calci	Osteo: Post A>Pre A
Caniggia et al. [67]	1990	270	Postmenopausal osteoporotic women	1–8 years	A) 1.0 μg/day Calci	Osteo: A>B
					B) Historical Controls	
Gallagher et al. [68]	1982	18	Postmenopausal osteoporotic women	6–8 months	A) 0.5 μg/day Calci	BFR: A>B
					B) Placebo	BRR: A<B
Inanir et al. [70]	2004	70	Postmenopausal osteoporotic women	6 months	A) 0.5 μg/day Calci + 1,000 mg calcium	PTH: NS
					B) 1,000 mg calcium	IL-1: A<B
						IL-6: NS
						TNF-α: A<B
Lambrinoudaki et al. [71]	2000	81	Premenopausal women with lupus	2 years	A) 0.5 μg/day Calci + 1,200 mg calcium	ALP: B>A, C
					B) Placebo Calci + 1,200 mg calcium	

Trial	Year	Number of participants	Study population	Trial duration	Treatments	Results
					C) Placebo Calci + Placebo calcium	
Ott et al. [72]	1989	86	Postmenopausal osteoporotic women	2 years	A) 0.43 μg/day Calci	PTH: NS
					B) Placebo	
Riggs et al. [73]	1985	56	Postmenopausal osteoporotic women	2 years	A) 0.5–0.75 μg/day Calci for 1 year	PTH: A<B, C
					B) 0.5–0.75 μg/day Calci for 2 years	HYP: A,B<C
					C) Placebo	
Sairanen et al. [74]	2000	51	Healthy postmenopausal women	4 years	A) 0.5 μg/day Calci + 800 mg calcium	Osteo: A<B
					B) 800 mg calcium	CTx: A<B
						PTH: A<B
Sambrook et al. [75]	2000	65	Cardiac or lung transplant patients	2 years	A) 0.5–0.75 μg/day Calci + 600 mg calcium for 1 year	Osteo: C>A,B
					B) 0.5–0.75 μg/day Calci + 600 mg calcium for 2 years	PICP: C>A,B
					C) Placebo + 600 mg calcium	CTx: C<A,B
Shane et al. [76]	2004	176	Cardiac transplant patients	1 year	A) 0.5 μg/day Calci	NTx: A,B<C
					B) 10 mg Alendronate	PTH: A<B,C
					C) Historical Controls	
Stempfle et al. [78]	1999	101	Cardiac transplant patients	3 years	A) 0.25 μg/day Calci + 1,000 mg calcium + HRT	NTx: A<B
					B) 1,000 mg calcium + HRT	PICP: NS
Tjellesen et al. [79]	1984	111	Healthy postmenopausal women	1 year	A) 0.25–0.5 μg/day Calci	ALP: B<A,C
					B) HRT	HYP: B<A,C
					C) Placebo	
Barone et al. [95]	2007	91	Postmenopausal osteoporotic women	1 year	A) 0.5 μg/day Calci + 70 mg alendronate	PTH: A<B
					B) 70 mg alendronate	
Cosman et al. [96]	1995	24	Postmenopausal osteoporotic women	5 days	A)1.0 μg/day Calci + HRT	ALP: NS
					B) HRT	CTx: NS
						HYP: NS
Eriksson et al. [97]	1993	22	Postmenopausal osteoporotic women	2 years	A)0.5 μg/day Calci + 500 mg calcium + calcitonin	PTH: A>B
					B) 500 mg calcium	
Gallagher et al. [53]	2001	489	Healthy postmenopausal women	3 years	A) 0.5 μg/day Calci	PTH: A,C<B,D

Trial	Year	Number of participants	Study population	Trial duration	Treatments	Results
					B) HRT	NTx: A,B,C<D
					C) 0.5 μg/day Calci + HRT	Osteo: B,C<A,D
					D) Placebo	
Gram et al. [98]	1998	48	Healthy men	1 week	A) 2.0 μg/day Calci	PTH: A,C<B,D
					B) Prednisolone	NTx: NS
					C) 2.0 μg/day Calci + Prednisolone	CTx: B,C<A,D
					D) Placebo	BSAP: A<B, C,D
						Osteo: B,C<A,D
Gutteridge et al. [99]	2003	66	Postmenopausal osteoporotic women	2 years	A) 0.5 μg/day Calci + HRT	Osteo: A<B
					B) HRT	
Rhee et al. [100]	2006	199	Postmenopausal osteoporotic women	6 months	A) 0.5 μg/day Calci + 5 mg alendronate	BSAP: A<B
					B) 0.5 μg/day alfacalcidol	NTx: A<B
Sambrook et al. [101]	1993	92	Patients on corticosteroid therapy	1 year	A) 0.6 μg/day Calci + 1,000 mg calcium + calcitonin	Osteo: A<B,C
					B) 0.6 μg/day Calci + 1,000 mg calcium	PTH: A,B<C
					C) 1,000 mg calcium	

> significantly (P<0.05) greater than, < significantly less than, *NS* no statistical difference, *Calci* calcitriol, *QD* once a day, *BID* twice a day, *QOD* once every other day, *PTH* parathyroid hormone, *NTx* cross-linked N-teleopeptide of type I collagen, *OSTEO* osteocalcin, *BSAP* bone-specific alkaline phosphatase, *CTx* cross-linked C-teleopeptide of type I collagen, *PICP* serum procollagen type I carboxyterminal propeptide, *BFR* bone formation rate, *BRR* bone resorption rate, *IL-1* interleukin 1, *IL-6* interleukin 6, *TNF-α* tumor necrosis factor alpha, *ALP* alkaline phosphatase, *HYP* urinary hydroxyproline

Table 3

Study characteristics of trials involving calcitriol, BMD, and fractures

Trial	Year	Number of participants	Study population	Trial duration	Treatments	Results
Aloia et al. [65]	1988	27	Postmenopausal osteoporotic women	2 years	A) 0.8 μg/day Calci + 800 mg calcium	BMD LS: A>B
					B) 400 IU/day Vit D + 800 mg calcium	BMD RAD: A>B
						Fractures: NS
Caniggia et al. [67]	1990	270	Postmenopausal osteoporotic women	1–8 years	A) 1.0 μg/day Calci	BMD TOT: A>B
					B) Historical Controls	Fractures: A<B
Inanir et al. [70]	2004	70	Postmenopausal osteoporotic women	6 months	A) 0.5 μg/day Calci + 1,000 mg calcium	BMD LS: A>B
					B) 1,000 mg calcium	BMD TROC: A>B
						BMD INT: NS
Lambrinoudaki et al. [71]	2000	81	Premenopausal women with lupus	2 years	A) 0.5 μg/day Calci + 1,200 mg calcium	BMD LS: A>B,C
					B) Placebo Calci + 1,200 mg calcium	BMD HIP: NS
					C) Placebo Calci + Placebo calcium	
Ott et al. [72]	1989	86	Postmenopausal osteoporotic women	2 years	A) 0.43 μg/day Calci	BMD LS: NS
					B) Placebo	Fractures: NS
Sairanen et al. [74]	2000	51	Healthy postmenopausal women	4 years	A) 0.5 μg/day Calci + 800 mg calcium	BMD HIP: A>B
					B) 800 mg calcium	BMD LS: NS
Sambrook et al. [75]	2000	65	Cardiac or lung transplant patients	2 years	A) 0.5–0.75 μg/day Calci + 600 mg calcium for 1 year	BMD FEM: B>A,C
					B) 0.5–0.75 μg/day Calci + 600 mg calcium for 2 years	BMD WARD: B>A,C
					C) Placebo + 600 mg calcium	BMD TROC: B>A,C
						BMD LS: NS
						Fractures: B<A,C
Shane et al. [76]	2004	176	Cardiac transplant patients	1 year	A) 0.5 μg/day Calci	BMD LS: B>A>C
					B) 10 mg Alendronate	BMD FEM: A,B>C
					C) Historical controls	BMD HIP: A,B>C
						Fractures: NS
Stempfle et al. [78]	1999	101	Cardiac transplant patients	3 years	A) 0.25 μg/day Calci + 1,000 mg calcium + HRT (HGO)	BMD LS: NS

Trial	Year	Number of participants	Study population	Trial duration	Treatments	Results
					B) 1,000 mg calcium + HRT (HGO)	
Ebeling et al. [82]	2001	39	Osteoporotic men	2 years	A) 0.5 μg/day Calci	BMD LS: NS
					B) 500 mg calcium	BMD FEM: NS
						Fractures: NS
Arthur et al. [83]	1990	10	Postmenopausal osteoporotic women	1 year	A) 0.5 μg/day Calci	BMD LS: NS
					B) 100,000 IU/week Vit D	
Dambacher et al. [84]	1997	31	Postmenopausal women	1 year	A) 0.5 μg/day Calci or 1.0 μg/day alfacalcidol	BMD TRA: Post A>Pre A
						BMD COR: Post A>Pre A
Falch et al. [85]	1987	86	Postmenopausal osteoporotic women	3 years	A) 0.5 μg/day Calci	BMC PROX: NS
					B) 400 IU/day Vit D	BMC DIST: NS
						Fractures: NS
Fujita et al. [86]	1990	596	Postmenopausal osteoporotic women	7 months	A) 0.5 μg/QD Calci	BMD TOT: NS
					B) 0.25 μg/BID Calci	
					C) 1.0 μg/day alfacalcidol	
Gallagher et al. [87]	1990	50	Postmenopausal osteoporotic women	2 years	A) 0.62 μg/day Calci + 600 mg calcium + 400 IU Vit D	BMD LS: A>B
					B) Placebo + 600 mg calcium + 400 IU Vit D	BMD TOT: A>B
						Fractures: NS
Mirzaei et al. [88]	2003	37	COPD patients with osteopenia or osteoporosis	1 year	A) 0.25 μg/day Calci	BMD LS: NS
					B) Untreated controls	BMD FEM: A>B
Need et al. [89]	1990	66	Postmenopausal osteoporotic women	15 months	A) 0.25 μg/day Calci + 1,000 mg calcium	BMD FOR: A, B>C
					B) 0.5 μg/day Calci + 1,000 mg calcium	
					C) 1,000 mg calcium	
Tilyard et al. [90]	1990	636	Postmenopausal osteoporotic women	1 year	A) 0.5 μg/day Calci	VERT HT: A>B
					B) 1,000 mg calcium	
Diaz et al. [91]	2008	24	Pediatric leukemia patients	1 year	A) 0.25–0.5 μg/day Calci + 500 mg calcium	BMD LS: NS
					B) 500 mg calcium	LBS BMD LS: A>B
Caniggia et al. [92]	1996	365	Postmenopausal osteoporotic women	1–14 years	A) 1.0 μg/day Calci	Fractures: A<B
					B) Historical controls	

Trial	Year	Number of participants	Study population	Trial duration	Treatments	Results
Gallagher et al. [93]	1989	62	Postmenopausal osteoporotic women	3 years	A) 0.5 μg/day Calci	Fractures: A<B
					B) Placebo	
Tilyard et al. [94]	1992	622	Postmenopausal osteoporotic women	3 years	A) 0.5 μg/day Calci	Fractures: A<B
					B) 1,000 mg calcium	
Barone et al. [95]	2007	91	Postmenopausal osteoporotic women	1 year	A) 0.5 μg/day Calci + 70 mg alendronate	BMD LS: A>B
					B) 70 mg alendronate	BMD HIP: NS
Eriksson et al. [97]	1993	22	Postmenopausal osteoporotic women	2 years	A)0.5 μg/day Calci + 500 mg calcium + calcitonin	BMD RAD: NS
					B) 500 mg calcium	BMD LS: NS
Gallagher et al. [53]	2001	489	Healthy postmenopausal women	3 years	A) 0.5 μg/day Calci	BMD LS: A,B,C>D
					B) HRT	BMD TOT: A,B,C>D
					C) 0.5 μg/day Calci + HRT	BMD FEM: B,C>A,D
					D) Placebo	
Gutteridge et al. [99]	2003	66	Postmenopausal osteoporotic women	2 years	A) 0.5 μg/day Calci + HRT	BMD TOT: A>B
					B) HRT	BMD HIP: A>B
						BMD LS: NS
						Fractures: NS
Rhee et al. [100]	2006	199	Postmenopausal osteoporotic women	6 months	A) 0.5 μg/day Calci + 5 mg alendronate	BMD LS: A>B
					B) 0.5 μg/day alfacalcidol	
Sambrook et al. [101]	1993	92	Patients on corticosteroid therapy	1 year	A) 0.6 μg/day Calci + 1,000 mg calcium + calcitonin	BMD LS: A, B>C
					B) 0.6 μg/day Calci + 1,000 mg calcium	BMD FEM: NS
					C) 1,000 mg calcium	BMD RAD: NS
Frediani et al. [102]	1998	120	Postmenopausal osteoporotic women	2 years	A) 0.5 μg/day Calci	BMD TOT: A,B,C>D
					B) 0.5 μg/day Calci + 10 mg alendronate	BMD LS: A,B,C>D
					C) 10 mg alendronate	BMD ARM: A,B,C>D
					D) 500 mg calcium	BMD LEG: A,B,C>D
						BMD PLV: A,B,C>D
						BMD TRK: A,B,C>D
Gurlek et al. [103]	1997	30	Postmenopausal osteoporotic women	1 year	A) 0.5 μg/day Calci + etidronate	BMD LS: NS
					B) 0.5 μg/day Calci	

Trial	Year	Number of participants	Study population	Trial duration	Treatments	Results
Jensen et al. [104]	1982	74	Postmenopausal osteoporotic women	1 year	C) 0.25 μg/day Calci + calcitonin A) 0.5 μg/day Calci B) HRT C) 0.5 μg/day Calci + HRT D) Placebo	BMC: B,C>A,D
Malavolta et al. [105]	1995	152	Postmenopausal osteoporotic women	9 months	A) 0.25 μg/QOD + 5 mg alendronate B) 5 mg alendronate + 500 mg calcium C) 500 mg calcium	BMD FEM: A,B>C BMD LS: A,B>C
Masud et al. [106]	1998	58	Postmenopausal osteoporotic women	1 year	A) 0.5 μg/day Calci + 400 mg etidronate B) 400 mg etidronate + 400 mg calcium	BMD LS: A>B BMD FEM: A>B

> significantly ($P<0.05$) greater than, < significantly less than, *NS* no statistical difference, *Calci* calcitriol, *QD* once a day, *BID* twice a day, *QOD* once every other day, *HGO* hypogonadism, *LBS* low baseline BMD, *BMC* bone mineral content, *BMD* bone mineral density, *LS* lumbar spine, *TOT* total, *FEM* femoral, *TROC* trochanter, *INT* intertrochanter, *RAD* radius, *FOR* forearm, *HIP* hip, *TRK* trunk, *PLV* pelvis, *ARM* distal radius, *LEG* legs, *VERT HT* vertebral height, *PROX* proximal, *DIST* distal, *COR* cortical, *TRA* trabecular