



Plain vitamin D or active vitamin D in the treatment of osteoporosis: where do we stand today?

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Abstract

Osteoporosis is a major cause of morbidity and mortality worldwide and its prevention in order to avert fractures was considered of great importance in maintaining well-being and independence among the elderly. Strategies for osteoporosis prevention are well delineated, but research shows that the treatment options offered today could still be improved. The role of plain vitamin D (cholecalciferol) in bone health and the prevention of osteoporosis are well documented; however, as a treatment for osteoporosis, either with or without calcium, it has been shown to be ineffective. This is due in part to the strong negative feedback mechanisms in place in vitamin D-replete patients. However, other factors linked directly to ageing such as oestrogen depletion, reduced kidney or liver function may also be involved in reducing the body's capability to activate plain vitamin efficiently. This is why active vitamin D analogues such as alfacalcidol, 1- α -(OH)D₃, are of clinical interest. Alfacalcidol requires only one hydroxylation reaction to become active 1,25-(OH)₂-vitamin D₃, and the 25-hydroxylase catalyzing this reaction is found in the liver and also interestingly in osteoblasts suggesting a local effect. Registered for use in postmenopausal osteoporosis, in most countries worldwide, alfacalcidol has also shown efficacy in glucocorticoid-induced and male osteoporosis. The present review provides compelling evidence for the efficacy of this compound in the treatment of osteoporosis and prevention of fractures both in monotherapy and when combined with other osteoporotic drugs where additive effects are clear. The safety profile of alfacalcidol is shown to be highly acceptable and it is considered less likely to induce hypercalcaemia than another more widely used analogue, calcitriol. Therefore, it remains unclear as to why alfacalcidol is not more widely used in clinical practice.

Keywords Osteoporosis · Vitamin D/analogues · Alfacalcidol · Calcium

Introduction

Spontaneous or low-trauma fractures are often one of the first signs of osteoporosis, a chronic, initially often silent disease, characterised by compromised bone strength, namely low bone density and weakened bone architecture [1]. Most commonly of the vertebrae, radius and hip, such fractures are a major cause of morbidity and mortality worldwide accounting for millions of disability-adjusted life years (DALYs) annually [2] and placing the healthcare budgets of every country under immense strain [3–5]. Osteoporosis occurs in all

populations and at all ages but is most prevalent in the elderly [1] especially in postmenopausal females [6]. These are both considered to be primary osteoporosis and are type II (age related) and type I (postmenopausal), respectively [1]. Secondary osteoporosis is osteoporosis occurring as a result of disease, medication and/or lifestyle [1]. Clinically, osteoporosis is diagnosed on the basis of a bone mineral density (BMD) assessment that is ≥ 2.5 standard deviations (SD) below the average value for healthy, young women [2]. This WHO definition was globally considered to provide the threshold for both diagnosis and intervention [2]. However, bone density as a measure was designed for epidemiological studies and its use as a marker for fracture in individuals and to measure treatment outcomes is disputed [7]. On an individual basis, many other factors may influence skeletal fragility including bone size, shape, micro-architecture and bone quality [8]. Guidelines suggest that BMD should be used in conjunction with the online assessment tools FRAX and QFracture to ascertain the true risk of fracture in an individual [9]. Due to its

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high morbidity, the prevention of osteoporosis and fractures is considered vital to the continued health, quality of life and independence of elderly people [2]. Yet while strategies for osteoporosis prevention are well delineated [6, 10], what really is the best treatment option?

Vitamin D₃ (cholecalciferol)

Vitamin D, first recognised in the 1930s, plays an important role in bone health [11]. Calcitriol, 1,25(OH)₂D, the active form of vitamin D, is essential for the active absorption of dietary calcium from the small intestine and its subsequent uptake into the bone. Vitamin D is synthesised in the skin; its precursor, 7-dehydrocholesterol, is converted by sunlight into pre-vitamin D₃, which then undergoes isomerisation into vitamin D₃ [12]. Once in the circulation the liver and kidney complete its conversion to the hormonal form 1,25-dihydroxyvitamin D₃ (1,25[OH]₂D₃) or calcitriol [11]. An adequate calcium and vitamin D intake are important throughout life to develop and maintain an optimal bone mass [6], with a daily intake of 600 IU of vitamin D being recommended for all age groups from 3 years old upwards [6].

The role of plain vitamin D (cholecalciferol) is well documented in the prevention and treatment of rickets and osteomalacia, which are both due to severe vitamin D deficiency, and consequent inadequate mineralisation of bone matrix [13]. Correcting any deficiency resolves both disorders [13]. However, in osteoporosis, despite an obvious tendency towards its use for both prevention and treatment, the results are not so easy to interpret [14, 15]. Although low serum levels of vitamin D are frequently reported in elderly patients with fractures and osteoporosis, they are often no lower than in people of a similar age with good skeletal health [13].

Menopause has a specific impact on vitamin D metabolism, impairing bone turnover and increasing the incidence of falls and fractures [16, 17]. In the initial phases of postmenopausal osteoporosis, renal activation of plain vitamin D is reduced due to oestrogen deficiency [18, 19] and parathyroid hormone suppression [20]. This leads to reduced production of calcitriol [21] and malabsorption of calcium from the intestine [22], leading to rapid bone loss [20], and a marked increase in falls and fractures [17, 23]. Nevertheless, despite low serum levels of 1,25(OH)₂D being measured in women with osteopenia or even osteoporosis [24], some studies of oral supplementation with plain vitamin D and/or calcium have shown no increase in BMD [25, 26] or decrease in fracture rates [27, 28], despite increased serum of 25(OH)₂D levels [26].

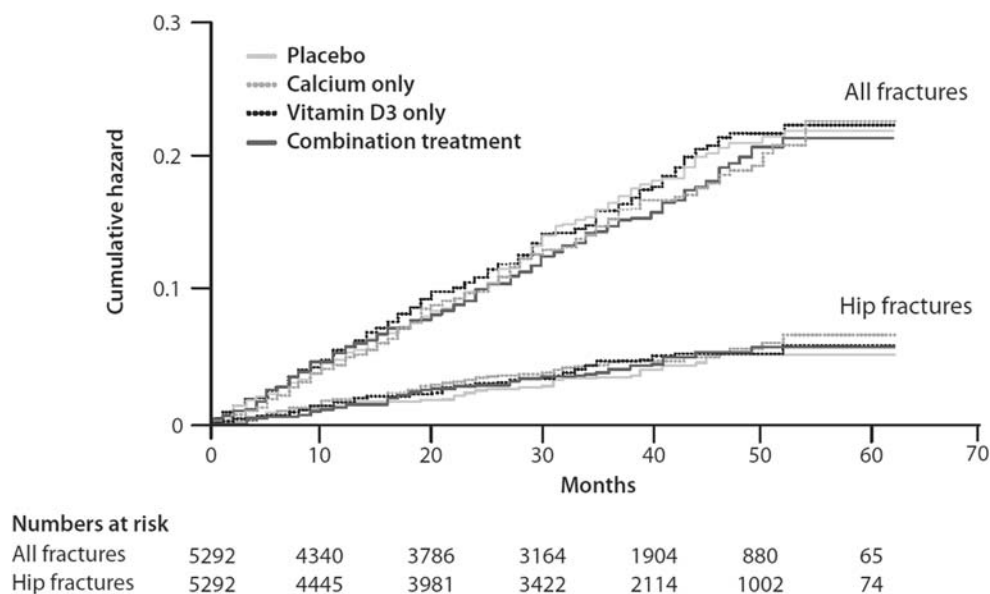
Why is plain vitamin D not effective in the treatment of osteoporosis?

As shown above, numerous clinical studies have indicated that plain vitamin D with or without calcium is not effective in the prevention or treatment of osteoporosis (see Fig. 1) [15, 25–28]. The reasons behind this are quite easily explained by an understanding of the strong negative feedback mechanism that occurs when serum 25(OH)D levels are replete [12]. When serum 1,25(OH)₂D increases, calcium absorption in the gut also increases. Once relatively high levels of serum calcium are reached, the secretion of PTH will decrease, leading to a lower production of the D-hormone, 1,25(OH)₂D [29, 30]. High serum 1,25(OH)₂D additionally inhibits both hepatic 25-hydroxylase and renal 1 α -hydroxylase, thus reducing the synthesis of both 25(OH)D and 1,25(OH)₂D. Plain vitamin D supplementation in patients with sufficient serum 25(OH)D, therefore, will not produce further calcitriol. Excess vitamin D will be stored in the fat tissue or in the liver [31–34].

Oral plain vitamin D supplementation in patients clinically deficient in serum 25(OH)D (< 50 nmol/L [20 ng/mL]) [12] may restore serum levels; however, osteoporosis endpoints are not necessarily improved (see Fig. 1) [27]. This may be a consequence of age-associated declines in hepatic and, even more, renal function, disease or pharmaceutical treatment all of which will effect hydroxylation [35]. In postmenopausal women, these problems are exacerbated further by oestrogen deficiency [18] and parathyroid hormone suppression [36], reducing the final renal activation of 25(OH)D even for patients with normal kidney function. The resulting deficiency of 1,25(OH)₂D in the circulation and at the target tissues will significantly affect the amounts of calcium and phosphate absorbed from the intestine and the homeostasis of mineralisation will become dysregulated as the skeleton becomes the body's major source of calcium [35]. Several drugs, commonly prescribed in patients at risk for osteoporosis, have direct effects on PTH levels. Loop diuretics such as bumetanide, furosemide, torasemide and calcium antagonists, of the dihydropyridine class, e.g. amlodipine and nifedipine, have been shown to result in raised levels of PTH and poorer skeletal measurements, while the use of thiazide diuretics is associated with more favourable skeletal outcomes, including a decrease in cortical bone loss, lowers PTH levels [37]. It has also been demonstrated that an annual, high-dose plain vitamin D substitution might actually increase the number of fractures and falls [38], but the mechanism by which this might occur is unknown.

A randomised, controlled study in 194 elderly women with vitamin D insufficiency conducted by Smith and colleagues in 2018 found there was no evidence of a threshold change in BMD despite increasing serum 25OHD or free 25OHD in a population treated with daily plain vitamin D doses of 400–

Fig. 1 Cumulative rates of all fractures and of hip fractures by a group. Numbers at risk of hip fracture are higher because they include participants who had another type of fracture, reproduced with permission from Grant 2005 [27]



4800 IU with calcium over a year [25]. These authors concluded that there was poor evidence to justify the routine use of plain vitamin D, with or without calcium, in the prevention and treatment of osteoporosis which was also the conclusion of a large meta-analysis published the same year [26]. This latter study examined 81 randomised controlled trials including a total of 53 537 participants and found reliable evidence that plain vitamin D supplementation does not reduce hip fractures [26]. It might therefore be concluded that there is little justification for the use of vitamin D supplements to maintain or improve musculoskeletal health in osteoporosis with or without the addition of calcium [26]. However, would using an active vitamin D analogue demonstrate any benefit? [39]

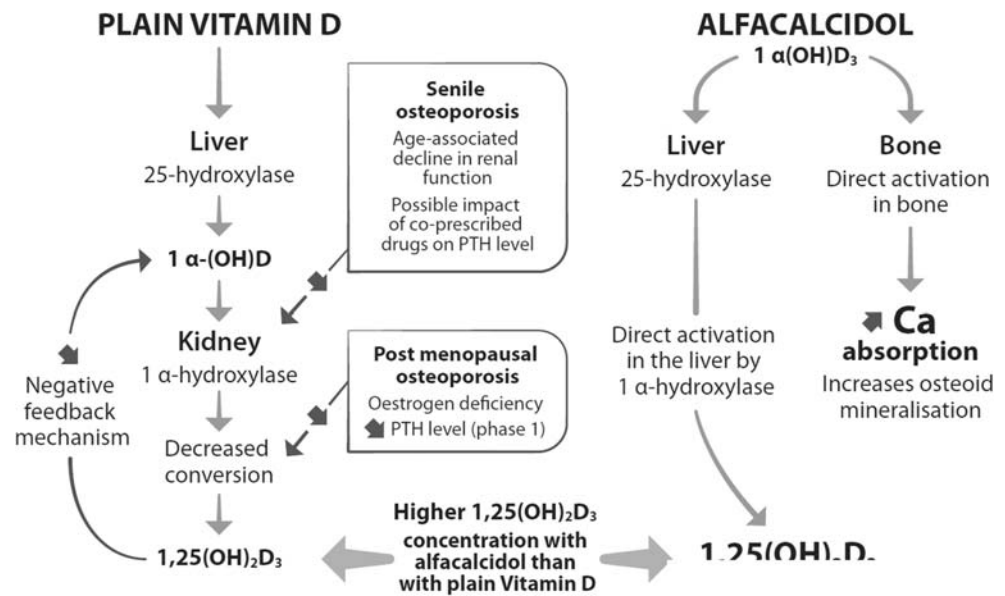
Alfacalcidol as an alternative to plain vitamin D

Alfacalcidol, $1\alpha(\text{OH})\text{D}$, is a potent vitamin D₃ analogue. Already activated at the crucial 1-position, it is converted rapidly and virtually completely in the liver to calcitriol, which is the active metabolite of vitamin D₃ important for demineralisation and remineralisation of bone tissue [40]. An early, large controlled clinical study showed that 3-year treatment with calcitriol ($0.25 \mu\text{g bd}$) resulted in a threefold reduction in the rate of new vertebral fractures in postmenopausal women compared with those who received 1 g of elemental calcium per day over the same period [41]. Alfacalcidol is approved for the treatment of different forms of osteomalacia (nutritional and malabsorptive, pseudo-deficiency and hypophosphataemic vitamin D resistant), postmenopausal, glucocorticoid-induced, male osteoporosis and senile osteoporosis in most countries worldwide [42, 43].

Alfacalcidol stimulates gastrointestinal absorption of calcium and phosphate and tubular reabsorption of calcium [42]. Via suppression of the parathyroid hormone, it reduces phosphate excretion in the urine [42]. Alfacalcidol is activated in the liver for systemic circulation and in osteoblasts for local $1,25(\text{OH})_2\text{D}$ activity [44]. It therefore has a pharmacokinetic profile which is independent of an individual's vitamin D status, age and kidney function [44]. This makes it possible to normalise or even increase calcitriol levels systemically and locally, thereby rapidly increasing the hormonal activity at different target tissues, with no interference from the negative feedback mechanism which regulates the activation of vitamin D under similar conditions (see Fig. 2) [45]. In patients with severe liver insufficiency, 25-hydroxylation of alfacalcidol, and of cholecalciferol, to $1,25(\text{OH})_2\text{D}$ may be reduced. A higher dosage may be necessary or alternative treatment should be proposed [46].

Alfacalcidol treatment may be considered as an active hormonal therapy [44]. While its alternative pathway for the activation to D-hormone may be superior to plain vitamin D in patients with a normal vitamin D status, it also creates controversy regarding its use, primarily because of fears that over time hypercalcaemia and/or hypercalciuria [44] could result in impairment of renal function and nephrocalcinosis [47]. The use of alfacalcidol, therefore, needs to be accompanied by frequent monitoring of serum and urine levels of calcium [47]. Dietary intake of calcium and the use of calcium supplements should be reviewed at the same time as any prescription of alfacalcidol [44]. Serum calcium should be measured before starting with alfacalcidol and after 3–6 months of therapy. If a clinically relevant increase in urinary or serum calcium is observed, this can be easily corrected by reducing the calcium supplementation (e.g. below 500 mg/day or by reducing alfacalcidol from 1 to 0.75 or from 0.75 to 0.5 g/day. The

Fig. 2 Comparison of activation pathways of plain vitamin D ((left) and alfacalcidol (right). Once ingested, alfacalcidol enters the blood circulation and 25-hydroxylation in the liver produces the active form of the D-hormone, $1,25(\text{OH})_2\text{D}_3$. Alfacalcidol activation is independent of vitamin D status, age and kidney function. Alfacalcidol can also be activated directly in the bone where it increases mineralisation locally



increased urinary or serum calcium should be always confirmed by a second measurement 1 week later [44]. It is important to mention that in daily practice, however, hypercalcaemia and hypercalciuria are extremely rare events.

The association of alfacalcidol and plain vitamin D could be advantageous in patients who have two vitamin D-related problems, both vitamin D deficiency and calcitriol hormone insufficiency, which is the case for 80% of patients undergoing dialysis [48]. Combinations of vitamin D3 (cholecalciferol) and an active calcitriol analogue, such as alfacalcidol, should be used to treat their vitamin deficiency. While such an approach may speculatively be of interest to correct vitamin D deficiency in types of cancer, auto-immune diseases, tuberculosis and cardiovascular disease [48], the use of such a combination is not recommended in any guidelines for osteoporosis. In osteoporosis, serum and urinary calcium have to be monitored from the onset with alfacalcidol and throughout treatment, the addition of cholecalciferol would increase the risk of hypercalcaemia with no clear clinical benefit.

There is clinical evidence to support the use of alfacalcidol in osteoporosis

Clinical trials of alfacalcidol have demonstrated its efficacy on all major endpoints used in trials of osteoporosis. A 2-year double-blind study in Japan compared the outcomes on the lumbar spine (L2-4) BMD, total BMD and fractures in 113 females with osteoporosis who received either 0.75 µg alfacalcidol or placebo per day both groups received calcium supplementation (calcium lactate 2.3 g/day [300 mg of elemental Ca^{2+}]) [49]. By 1 year, statistically significant differences were apparent between the two groups which led to the

conclusion at the end of the trial that alfacalcidol increased lumbar BMD ($p < 0.05$) and inhibited the decrease in total body BMD ($p < 0.001$) [49]. Although not reaching significance, there was a marked difference in new fracture occurrence between the two groups. Patients receiving alfacalcidol experienced approximately a third of the number of new fractures of those in the control group [49]. No safety concerns from elevated calcium levels were reported by these authors [49]. These positive effects are likely to be correlated to the higher levels of intestinal calcium absorption observed with alfacalcidol compared with plain vitamin D [50]. Short-term treatment of elderly osteoporotic women with low-dose alfacalcidol (0.5 µg/day) was shown to increase calcium absorption, decrease PTH and reduce bone resorption resulting in a positive effect on bone turnover [51, 52].

The efficacy of alfacalcidol has been directly compared with that of plain vitamin D in three studies shown in Table 1. Two of these were in patients with postmenopausal osteoporosis [39, 50] and in the third from glucocorticoid-induced osteoporosis, alendronate [53]. Doses of alfacalcidol were from 0.5–1 µg/day and in all cases showed a statistically significant improvement of osteoporosis endpoints, calcium absorption [50], lumbar BMD [39, 53] and reduction in the frequency of new fractures [53] in favour of alfacalcidol.

Additive effects are seen when alfacalcidol is used in combination with other anti-osteoporosis drugs

Several actions have been described for alfacalcidol or its end product calcitriol. These include effects on the gut, parathyroid glands and bone amongst other tissues [44]. Alfacalcidol stimulates calcium absorption [50] and osteoblast activity [20]

Table 1 Results from three randomised trials that compared the effects of alfacalcidol with either vitamin D in monotherapy or in combination with calcium on osteoporotic endpoints, calcium absorption, lumbar BMD and fractures [39, 50, 53]

Criteria	Type of osteoporosis	N° of participants	Duration	Treatments	Results	<i>p</i> value
Mean intestinal calcium absorption [50]	Postmenopausal osteoporosis	46 women with radiological evidence of vertebral osteoporosis	6 months	(1) Alfacalcidol: 0.25/μg twice daily vs (2) vitamin D ₂ 500–1000 units daily	Mean intestinal calcium absorption at M6: Alfacalcidol: 0.68 Vitamin D ₂ : 0.48 (fraction of dose per hour)	<i>p</i> < 0.05 in favour of alfacalcidol
BMD [39]	Postmenopausal osteoporosis	148 postmenopausal osteoporotic women	18 months	(1) Alfacalcidol 1 μg/day vs (2) vitamin D ₃ 880 IU plus calcium once daily	Lumbar BMD at M18: Difference from baseline Alfacalcidol: 0.021 g/cm ² Vitamin D ₃ +Ca: 0.005 g/cm ²	<i>p</i> < 0.005 in favour of alfacalcidol
BMD and fractures [53]	Established glucocorticoid--induced osteoporosis	105 patients with established GIOP	36 months	(1) Alfacalcidol 1 μg + 500 mg calcium/day vs (2) vitamin D ₃ 1000 IU + 500 mg calcium/day	% change BMD of the lumbar spine at M36: Alfacalcidol: + 2.4% Vitamin D ₃ +Ca: - 0.8% % of patients with at least one new fracture at M36: Alfacalcidol: 19.4% Vitamin D ₃ +Ca: 40.6%	<i>p</i> < 0.0001 in favour of alfacalcidol <i>p</i> < 0.001 in favour of alfacalcidol

which works synergistically with the suppression of osteoclast activity [20, 54] and bone resorption [39, 55]. This wide range of different actions has raised interest in the use of alfacalcidol as a partner for osteoporosis drugs with a single mode of action that is to say acting only on bone turnover [44].

First-line pharmacological treatment of osteoporosis of any type typically relies on bisphosphonates, such as alendronate and risedronate [56]. This class of drugs decreases bone resorption through suppression of osteoclast activity and alendronate has been shown to both increase bone mineral density at different skeletal sites and reduce fracture incidence [57]. Plain vitamin D has been routinely added to antiresorptive or bone anabolic therapy in several pivotal trials where cholecalciferol and calcium supplementation for all enrolled participants included [58–60] in addition to alendronate or just for those participants who had calcium intakes less than 1000 mg/day [61–63]. However, no head-to-head study has been performed to see if the combination of drugs results in superior clinical outcomes and as discussed above, plain vitamin D alone has demonstrated contradictory results for preventing falls and fractures [38].

Studies of alfacalcidol in combination with frequently used osteoporotic agents [47] that have been performed to date are discussed below [44, 57, 64–66].

A synergistic action between bisphosphonates and alfacalcidol has long been considered to be due to additive

effects for bone turnover [67], and numerous publications testify to the research effort in this area [57]. One of the largest trials performed was by Orimo and colleagues [68] who enrolled over 2000 patients and showed that the combination of alfacalcidol and alendronate was no more effective for overall vertebral fracture prevention. However, subgroup analysis demonstrated that it was more effective for fracture prevention in patients with severe vertebral deformity, multiple prevalent vertebral fractures, and for non-vertebral weight-bearing bone fracture prevention [68].

However, the most convincing evidence for this synergistic effect comes from a network meta-analysis performed by Shao [57] in which data from over 3700 osteoporosis patients from 13 RCTs were included. Nine trials were conducted in Japan, two in Germany, one in China and one in the Netherlands. The combination of alendronate and alfacalcidol was shown to be significantly better in preventing bone fractures than alendronate alone (OR = 0.53, 95% CI: 0.19–0.95) or alfacalcidol (OR = 0.25, 95% CI: 0.08–0.49) when used as monotherapy [57]. This superior efficacy when alendronate and alfacalcidol are combined may be based on their different but complementary modes of action [57].

A study which comprised three arms, in patients with established postmenopausal or male osteoporosis, found that alfacalcidol in combination with alendronate had statistically significant superior efficacy versus plain vitamin D in

combination with the bisphosphonate or alfacalcidol alone for the total number of new fractures either vertebral or non-vertebral. This study also showed that 80% of patients with alfacalcidol in combination with alendronate were free of back pain after 2 years of the trial compared to 30% of those taking alendronate with plain vitamin D, $p < 0.003$ [65].

In Europe, one of the most commonly used treatments for postmenopausal osteoporosis is raloxifene, a selective oestrogen which inhibits bone resorption [56].

Its ability to reduce the risk of vertebral fractures has been demonstrated [69] but its efficacy with non-vertebral and hip fractures has not been evaluated adequately [56]. A Japanese group studied the effect of daily alfacalcidol (1 µg) in combination with raloxifene (60 mg) compared with raloxifene (60 mg) alone in a group of 169 women with postmenopausal osteoporosis or osteopenia for 2 years [70]. Lumbar bone density increased in both groups with no statistical difference between groups at the end of the trial. However, in those women treated with raloxifene and alfacalcidol, a greater bone-sparing effect from the suppression of the secondary increment of serum PTH was seen, then when raloxifene was used alone [70].

Hormone replacement therapy (HRT) covers a wide range of oestrogen or oestrogen plus pro-oestrogen combinations. Oestrogens clearly reduce the negative effects of menopause on bone turnover; nevertheless, their use in treating osteoporosis is limited because of the possibility of side effects associated with oestrogen supplementation [71]. The utility of HRT is therefore limited to younger postmenopausal women at high risk of bone fracture [47]. As reduced calcium absorption in older women also contributes to osteoporosis, there is a strong hypothetical basis for testing a combination of low-dose HRT and alfacalcidol at 1.0 µg/day. Such a study performed in 83 females (≥ 60 years old, BMD of -1.0 SD) who were randomly assigned to receive 0.31 mg equine oestrogen (CEE) and 2.5 mg of medroxyprogesterone acetate (MPA) either with or without alfacalcidol at 1.0 µg/day for 24 months [72]. Results at 24 months showed that the addition of alfacalcidol to HRT significantly increased lumbar spine BMD compared with HRT alone [72]. This difference was observed from 6 months of treatment and it was equally apparent that alfacalcidol significantly increased serum calcium levels while decreasing PTH. As secondary hyperparathyroidism from increased calcium levels during HRT therapy is thought to reduce the effectiveness of HRT on osteoporosis, the addition of an active vitamin D analogue such as alfacalcidol to a low-dose HRT regimen may be a way to overcome this [72]. As the side effects from HRT are dose dependent [71], the combination of low-dose HRT with alfacalcidol increases the therapeutic options for elderly women at high risk of osteoporotic fracture [72].

Osteoclast differentiation, activation and survival are dependent on the receptor activator of nuclear factor NFκB

(RANK) and its ligand RANKL [55]. A high affinity, human monoclonal antibody, denosumab (DMAb) developed against RANK has been used successfully in the treatment of postmenopausal osteoporosis [47]. Three years of treatment comprising 60 mg 6 monthly subcutaneous injection of denosumab was shown to result in a 68% reduction in the incidence of new vertebral fractures, a 20% reduction in non-vertebral fractures and a 40% reduction in hip fractures [58]. While most studies of denosumab have been carried out in combination with plain vitamin D and calcium, a 12-month retrospective study compared the effects of denosumab in combination with alfacalcidol versus denosumab and plain vitamin D [55]. Postmenopausal women with a mean age > 75 years old received 60 mg denosumab subcutaneously every 6 months either in combination with orally administered cholecalciferol (10 µg) and calcium (610 mg/day) ($n = 60$) or with oral alfacalcidol, 0.8 ± 0.0 (0.25–1.0) µg, and a calcium formulation, 99.2 ± 8.5 (0–260) mg/day, ($n = 67$) which was used at each physician's discretion [55]. Both groups experienced a significant increase in BMD at the lumbar spine and total hip which was seen from 6 months onwards; however, only in the group with alfacalcidol was a significant increase in BMD observed at the femoral neck, $p < 0.001$ from both baseline and the plain vitamin D group at 6 months and 12 months. The alfacalcidol group also experienced an increase in BMD at the distal forearm which gained statistical significance from the baseline and the plain vitamin D group at 12 months ($p < 0.1$) [55]. Between the two groups, the only serum marker to show a statistical difference was intact PTH which was decreased in the DMAb plus alfacalcidol group from baseline to 6 months (38.2 pg/mL vs. 32.8 pg/mL, $p < 0.001$) and 12 months (38.2 pg/mL vs. 30.4 pg/mL, $p < 0.001$) [55]. Increased serum PTH causes an increase of bone turnover and bone resorption which is usually associated with (primarily cortical) bone loss [73].

While it might appear that the action of alfacalcidol to stimulate calcium absorption [50] and osteoblast activity [74] which works synergistically with the suppression of osteoclast activity [20, 54] and bone resorption [39, 55] exhibited by these other osteoporotic drugs to further increase BMD [20, 75] and reduce fractures [74–76], there is still an open question amongst physicians as to its safety compared with plain vitamin D [45, 47, 56].

The safety of alfacalcidol compared with that of plain vitamin D

The major debate surrounding the use of active vitamin D derivatives such as alfacalcidol and calcitriol is the perceived risk of hypercalcaemia and hypercalciuria [45, 47, 56]. Adverse effects associated with prolonged hypercalcaemia may include impaired renal function and nephrocalcinosis

[47]. While fully aware of this concern, the personal opinion of the author from his longstanding clinical experience with alfacalcidol, one of the first active analogues to be synthesised [45], is that it can be used in all confidence based on many years of post-marketing approval usage. Common side effects, as published by the manufacturer, include at a frequency $\geq 1/100$ to $< 1/10$, rash, hypercalcaemia, hyperphosphataemia and hypercalciuria [40]. Clinical studies of alfacalcidol in monotherapy, or in combination, have routinely found no serious side effects [77–79] and a similar safety profile to plain vitamin D3 [55, 80]. There is in fact a lower risk of developing hypercalcaemia and/or hypercalciuria with alfacalcidol than calcitriol because the need for a further liver hydroxylation step retards the plasma concentration curve compared with that of calcitriol [45]. After the ingestion of calcitriol, there is a primary effect of increasing small intestinal calcium resorption and then immediate absorption of the hormone which produces a plasma peak associated with a higher risk of calcium metabolism disorders [45]. Because of this pharmacokinetic profile, alfacalcidol is considered safer than calcitriol as regards the risk of these undesirable events [81]. Due to the greater increases in BMD and reductions seen in fracture incidence, the risk-benefit ratio of alfacalcidol is generally regarded as being advantageous compared with plain vitamin D [80]. Nevertheless, it is recommended that serum and urinary calcium be monitored at onset and during alfacalcidol treatment with immediate withdrawal of treatment for ~ 7 days until clinical symptoms, or biochemical evidence of hypercalcaemia, or idiopathic hypercalciuria are resolved [40]. Use in patients with existing hypercalcaemia (i.e. primary hyperparathyroidism) or idiopathic hypercalciuria is contraindicated [40] while in patients with normocalcaemic hyperparathyroidism, its use may be encouraged.

There is little clear evidence as to the effects of calcium supplementation of the diet while using alfacalcidol. Consequently, it is for the physician to prescribe based on experience and individual patient needs. However, the general consensus is that supplementation should be avoided or, if necessary, used with care [45]. The author always used in studies or clinical practice 1 μg alfacalcidol and 500 mg calcium per day. Used at the recommended dosage, with adequate patient monitoring, there should be no safety concerns from the use of alfacalcidol [40].

Alfacalcidol in treatment guidelines

Alfacalcidol is amongst the active vitamin D analogues registered in most countries worldwide for postmenopausal osteoporosis with data that also show its efficacy also in glucocorticoid-induced [75] and in male osteoporosis [43]. Daily oral administration is recommended at 1 $\mu\text{g}/\text{day}$. While widely used and studied in Japan and China [57, 72, 77, 79, 82], low recognition

of its advantages exists in Europe and North America. Its use is, however, included in wider international guidelines for the diagnosis, management and treatment of osteoporosis and established postmenopausal osteoporosis [45, 47].

Conclusions

While the above evidence clearly supports the superiority of alfacalcidol over plain vitamin D in the treatment of osteoporosis, there still remain several unanswered questions as to why it is not used more frequently in clinical practice. Plain vitamin D itself, with or without calcium, is not useful in either the prophylaxis or treatment of osteoporosis in subjects who are replete in vitamin D. A recent meta-analysis showed that poor evidence to justify the routine use of plain vitamin D in osteoporosis prevention [26]. Nevertheless, this is not always reflected in current treatment guidelines. The latest NOGG guidelines recommend that in postmenopausal women and men ≥ 50 years who are at increased risk of fracture, a daily dose of 800 IU of plain vitamin D should be advised (grade A recommendation) [56]. While these guidelines also consider calcitriol as an analogue alternative to plain vitamin D, there is no mention of alfacalcidol, although alfacalcidol is considered safer than calcitriol in regard to the risk of undesirable events, i.e. hypercalcaemia and hypercalciuria [81], and despite a plethora of studies carried out in the 1980s and 1990s that have repeatedly shown the efficacy of alfacalcidol in osteoporosis [78, 82]. When added to the results from newer studies of alfacalcidol in both monotherapy and in combination discussed in this review, the wealth of data leads the author to an unresolved question; what more needs to be done to advance the use of alfacalcidol in current practice?

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