The role of alfacalcidol

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Summary

Alfacalcidol (1 alpha-hydroxy vitamin D3) is a synthetic vitamin D analogue which does not need to pass through kidneys for hydroxylation. It is hydroxylated fully in the liver and bone at position 25 to 1,25 (OH)2D3. Preclinical studies have suggested the superiority of alfacalcidol on both bone metabolism and osteoporosis treatment compared to plain vitamin D. Alfacalcidol has been shown to increase BMD by ameliorating intestinal calcium absorption and/or directly affecting bone cells and this effect is particularly evident when given in combination with anticatabolic drugs. Alfacalcidol seems to have additional preventive effects against the risk of falling, probably due to a direct action on the specific muscle receptor. In fact, in elderly sarcopenic patients alfacalcidol may improve the balance so reducing the risk of falls and, consequently, also the risk of fracture. Moreover, 1-alpha-calcidol is indicated in conditions of deficiency of the enzyme 1 alpha hydroxylase (eg, moderate-to-severe renal insufficiency, hypoparathyroidism and mutations in the gene encoding the enzyme 1-alpha-hydroxylase) and of intestinal malabsorption. However, at present, the efficacy of alfacalcidol in reducing osteoporotic fractures has not yet been defined. More data from randomized controlled trials are warranted in order to better define the role of alfacalcidol in the therapeutical strategies for osteoporosis.

KEY WORDS: alfacalcidol; vitamin D; osteoporosis; sarcopenia.

Effects on alfacalcidol on bone tissue

Many epidemiological studies have reported that vitamin D deficiency and insufficiency is a global health issue that afflicts more than one billion children and adults worldwide (1, 2). Vitamins D2 (ergocalciferol) and D3 (cholecalciferol) are produced by the skin or absorbed from the gut. They are metabolized into their active form, calcitriol, by two successive steps: 25-hydroxylation in the liver to 25(OH)D, followed by 1α-hydroxylation in the renal proximal tubules to 1,25-(OH)2D. Some other cells exhibit 1α-hydroxylase activity, including osteoblasts, placental cells, macrophages and monocytes (1).

The biologically active vitamin D, 1,25(OH)2D, acts in the intestine to stimulate calcium (Ca) absorption and maintain Ca balance. Under conditions of vitamin D insufficiency [25(OH)D serum levels < 30 ng/ml] or deficiency [25(OH)D serum levels< 20 ng/ml] intestinal Ca absorption decreases resulting in a compensatory increase in parathyroid hormone (PTH) levels (secondary hyperparathyroidism) which stimulates not only the activation of vitamin D to 1,25(OH)2D but also bone resorption. Elderly people are at risk of vitamin D deficiency and insufficiency, because of their reduced mobility and consequent decreased exposure to sunshine. Also the capacity of the skin to synthesize vitamin D can decrease twofold with age (3, 4). In the presence of inadequate vitamin D status, calcium absorption is lower than optimal and there is increased bone resorption and accelerated bone loss (5).

Alfacalcidol (1 alpha-hydroxy vitamin D3) is a synthetic vitamin D analogue which contains a hydroxyl group in position 1 and, therefore, does not need to pass through kidneys for hydroxylation. It is hydroxylated fully in the liver and bone at position 25 to 1,25 (OH)2D3 (calcitriol) (Figure 1).

Numerous preclinical studies have suggested the superiority of alfacalcidol on both bone metabolism and osteoporosis treatment compared to plain vitamin D. This superiority may be due to the fact that alfacalcidol acts on bone tissue independently of PTH suppression and vitamin D supply (6). In fact, alfacalcidol, besides inducing a dose-dependent suppression of bone resorption, is also able to stimulate bone formation so increasing both bone mineral density and mechanical resistance, especially at the cortical level (7). Furthermore, alfacalcidol acts independently of the negative feedback signal necessary for the activation of other vitamin D metabolites, thus guaranteeing normal efficacy even in subjects with reduced renal function as frequently happens in subjects with a more advanced age (8, 9). A recent study has reported that in osteoporotic postmenopausal women a 4-week treatment with alfacalcidol (1μg/day) significantly increased by 45.9% (27.9 to 63.8%) the intestinal fractional calcium absorption as assessed by using a double isotope method, whereas no significant changes in intestinal fractional calcium absorption were observed in women treated with vitamin D3 (800 IU/day) (10). Moreover, alfacalcidol, requiring 25-hydroxylation at the hepatic level to be active, displays a retarded plasma curve with respect to calcitriol with a consequent lower risk of developing hypercalcaemia and hypercalciuria.

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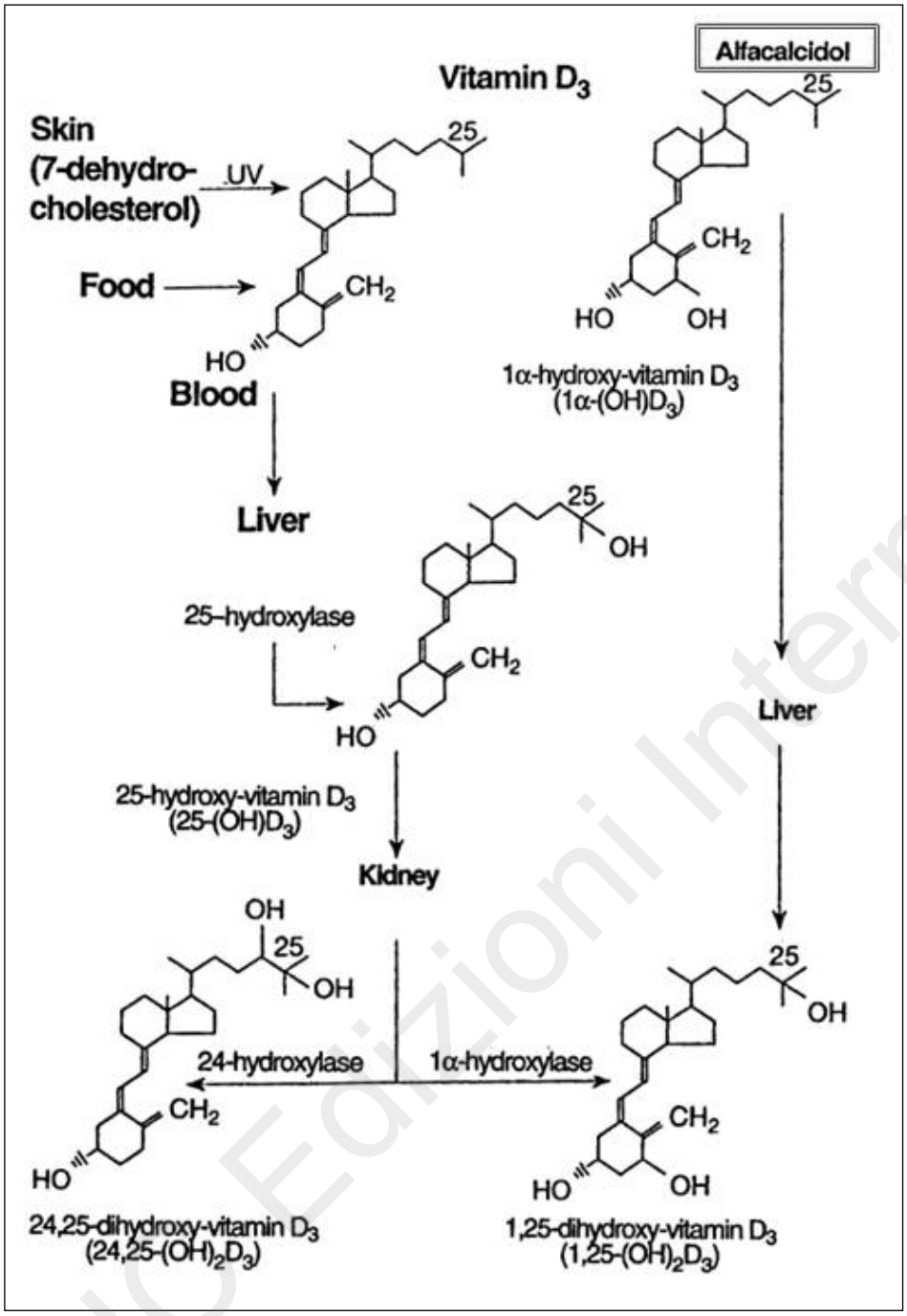

Figure 1 - Comparison of the two-step activation pathway of vitamin D3 and the direct activation of alfacalcidol to form 1,25-(OH)2-D3.

Extraskeletal effects

It is well known that vitamin D, apart from the effect on bone, may cause many extraskeletal effects. Among the extraskeletal effects of vitamin D, the most important one is definitely the positive action on muscle tissue. In fact, vitamin D has direct effects on muscle strength, probably modulated by specific vitamin D receptors present in human muscle tissue. Lower circulating 25(OH)D levels are associated with a reduction in muscle mass and increasing levels of frailty and may contribute to the mechanisms leading to an increase in risk of falls and fractures (11, 12).

There are numerous studies which show how the administration of alfacalcidol improves muscle function. In particular, alfacalcidol is able to activate some calcium transport mechanisms at the level of the muscular sarcoplasmic reticulum, essential in muscle contraction. The effects of alfacalcidol on muscles could also be due to the *de novo* protein synthesis, which would affect muscle cell growth via highly specific nuclear receptors. It has been reported that treatment with alfacalcidol increases both the number and the diameter of type II muscle fibres, as measured using muscle biopsies. In fact, in a study carried in elderly women, it was observed that the treatment with alfacalcidol, already after 3 months, increased the relative number and the size of the type II muscle fibres (13, 14).

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The efficacy of alfacalcidol in reducing the risk of falls was evaluated in a 36-week double-blind, placebo-controlled, randomized trial by Dukas et al. (15). In this study, elderly participants (n=410), aged 70 years or over, were randomly assigned to 1 µg/day alfacalcidol or matching placebo; this study showed that treatment with alfacalcidol significantly reduced the number of fallers and the number of falls in an elderly population with a minimum calcium intake of 512 mg/d or more, independently of calcium intake (15).

Sarcopenia, or the age-related decrease in muscle strength and mass, is an important risk factor for osteoporosis and disability in elderly subjects. Recently, there has been a growing interest in the use of vitamin D in sarcopenic subjects; in fact, sarcopenia is characterized by the loss mainly of type 2 muscle fibres on which vitamin D has been reported to have a protective effect. A Japanese study by Ito et al. (16) reported that in elderly women with low muscle mass 1-year treatment with alfacalcidol (0.5-1µg/day) significantly increased muscle mass, as assessed by appendicular SMI (skeletal muscle index) by DXA. Therefore, the use of alfacalcidol seems to have additional preventive effects against the risk of falling, probably due to a direct action on the specific receptor on the muscle cells. Since muscle mass and muscle strength are positively correlated, it has been hypothesized that in elderly sarcopenic patients alfacalcidol may improve the balance and reduce the risk of falls and, consequently, also the risk of fracture (16).

Clinical use of alfacalcidol

Appropriate supplementation with calcium and vitamin D is an integral part of any therapeutic strategy of osteoporosis. Preclinical studies have suggested the superiority of alfacalcidol on both bone metabolism and muscle strength compared to plain vitamin D. Alfacalcidol is registered in Europe for postmenopausal osteoporosis and renal bone disease; however, literature data have shown the efficacy of alfacalcidol also in glucocorticoid-induced and male osteoporosis. For alfacalcidol daily oral administration is recommended, being 1 µg/day the mostly used regimen (17). Although the efficacy of alfacalcidol in reducing osteoporotic fractures has not yet been defined, alfacalcidol may be of considerable importance when used in combination with anti-resorptive drugs. The combination of risedronate and alfacalcidol, even at sub-therapeutic doses, is able to determine an improvement in the mechanical and biochemical characteristics of the bone with respect to the administration of risedronate alone. Several studies have assessed the additive impact of alfacalcidol on bone mineral density and on bone strength in postmenopausal women treated with alendronate. In particular, in the AAC-Trial (Alfacalcidol-Alendronate-Combined) 90 patients with established osteoporosis (57 women and 33 men) were allocated to three treatment arms (alfacalcidol plus calcium, alendronate plus plain vitamin D and Ca, and alendronate plus alfacalcidol and Ca). During the 2-year-study period significantly ($p < 0.001$) higher increases in BMD at lumbar spine and at total hip in the combined treatment group were observed. The number of patients with new vertebral and non-vertebral fractures after 2 years was 9 with alfacalcidol alone, 10 with alendronate and plain vitamin D and 2 only in the group receiving alendronate plus alfacalcidol ($p < 0.02$) (18).

More recently, Felsemberg et al. in a 36-month randomized, double-blind study, carried out on a large cohort of postmenopausal women with reduced bone mass, found that combined administration of alendronate (70 mg/week) and alfacalcidol (1 µg/day) significantly increased tibia trabecular and cortical density and also the strength of the tibia (assessed by pQCT) with respect to alendronate plus placebo (199).

In another Japanese study 53 postmenopausal women with osteoporosis were allocated to an 18-month treatment with either ibandronate (1 mg iv monthly) or ibandronate plus alfacalcidol (1 µg/day). The patients treated with ibandronate plus alfacalcidol showed a greater reduction in bone turnover markers and a greater increase in BMD both at lumbar spine (6.6 *vs* 3.4%; P<0.05) and total hip (4.8 *vs* 3.2%; p<0.05) with respect to those treated with ibandronate alone (20).

In a recent study by Ebima et al. (21) 127 postmenopausal women with osteoporosis, (mean age 75.6 years), were allocated to a 12-month treatment with either denosumab 60 mg every 6 months plus cholecalciferol 10 µg/day and calcium 600 mg/day (n=60) or denosumab 60 mg every 6 months plus alfacalcidol 0.8 µg/day and calcium 100 mg/day (n= 67). At the end of the 12-month study period the changes in BMD were significantly higher in the patients treated with alfacalcidol with respect to those treated with plain vitamin D at both femoral neck and distal radius (4.9 *vs* 1% and 3.9% *vs* 0.8%, respectively). No significant differences between the two groups for BMD at lumbar spine and total hip were observed, whereas serum PTH levels were significantly lower in the denosumab plus alfacalcidol (47.6 pg/mL *vs* 30.4 pg/ mL, p< 0.001).

These results suggest that the efficacy of the antiresorptive/ alfacalcidol combination on both BMD and fracture risk can be explained by the synergism of the mechanisms of action of the two drugs. In fact, the antiresorptive effect of this combination was mainly explained by the action of alfacalcidol in preventing secondary hyperparathyroidism which reduces the response to anticatabolic drugs; moreover, these data could indirectly confirm the stimulating effect of alfacalcidol on osteoblasts observed in preclinical studies on ovariectomized rats.

Conclusions

Alfacalcidol has been shown to increase BMD by ameliorating intestinal calcium absorption and/or directly affecting bone cells and this effect is particularly evident when given in combination with anticatabolic drugs. Alfacalcidol seems to have additional preventive effects against the risk of falling, probably due to a direct action on the specific muscle receptor. Moreover, in elderly sarcopenic patients alfacalcidol may improve the balance so reducing the risk of falls and, consequently, also the risk of fracture. Alfacalcidol is also indicated in conditions of deficiency of the enzyme 1 alpha hydroxylase (e.g., moderate-to-severe renal insufficiency, hypoparathyroidism and mutations in the gene encoding the enzyme 1-alpha-hydroxylase) and of intestinal malabsorption, two common conditions often under diagnosed especially in elderly populations. However, on the basis of the results of more recent metanalyses, the efficacy of alfacalcidol in reducing osteoporotic fractures has not yet been defined (22). Therefore, more data from randomized controlled

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trials are needed to clarify the efficacy of alfacalcidol in reducing fragility fracture risk in order to better define its role in therapeutical strategies for osteoporosis.

Conflict of interest

Ranuccio Nuti and Carla Caffarelli declare that they have no conflict of interest.

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