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The effect of Vitamin D on falls and fractures

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Abstract

Vitamin D (cholecalciferol) is important for normal development and maintenance of the skeleton. The metabolites 25(OH)D and 1,25(OH)$_2$D are not only important for treating rickets and osteomalacia but also for all types and clinical stages of osteoporosis. Patients with low calcium intake and a low vitamin D status are at risk to develop secondary hyperparathyroidism, increased bone resorbtion, osteopenia and fractures. This can be counteracted by a lifelong sufficient vitamin D supply plus dietary or supplementary calcium. The effects of vitamin D on muscle, balance and cognitive functions may be an added value in fracture prevention. Today it is generally accepted that a supplementation with vitamin D and calcium should be added to every specific medical treatment of osteoporosis. In contrast to this general recommendation the potency of vitamin D alone with or without calcium to reduce the incidence of falls and/or fractures is still a debated controversy. Studies and meta-analyses during the last two decades on the effect of vitamin D and calcium supplements have not resolved the controversy on the risk of falls and fractures in healthy or osteopenic elderly populations. A thorough analysis of these trials supports our clinical experience that the efficacy of vitamin D-calcium supplementation depends on factors related to patient selection, medical intervention and study design, e.g. age, mobility, preventing falls and fractures, co-morbidity, initial vitamin D status and renal function. We conclude that plain vitamin D (cholecalciferol) with sufficient calcium intake is able to reduce the risk of falls and fractures only when adopting optimal selection criteria for patients and study conditions.

Key Words: *falls, fractures, muscle weakness, osteoporosis, renal function, VDR vitamin D receptor*

Introduction

Vitamin D (cholecalciferol/ergocalciferol) was detected in the first decades of the last century as a substance for curing rickets [1–3]. Only in the sixties it was shown that this "vitamin" is indeed a pro-hormone that has to be activated in two steps to become an active hormone (1,25-dihydroxy-cholecalciferol = calcitriol) [4]. Due to the historical relation of vitamin D to rickets in children and osteomalacia in adults the prevailing views that vitamin D plays no role in osteoporosis persisted for some decades.

A break through was the "Landmark publication" from the group of Pierre Meunier in 1992 showing that in elderly, ambulatory women a simple supplementation with 800 IU vitamin D plus 1,200 mg calcium over 18 months reduced the risk of hip fractures by 43 % and of other non-vertebral fractures by 32 % [5].

In the scientific community these data induced a general astonishment. Why had this treatment been so effective? It was speculated that the participating elderly French ladies (mean age 84 years) must have been all vitamin D deficient. The fact that in this particular study calcium-phosphate had been used instead of the mostly used calcium-carbonate was discussed as another potential factor contributing to these excellent fracture results. Only in later studies phosphate deficiency due to low dietary supply or to intestinal phosphate binding by too high calcium supplements in the very elderly was identified as a possible risk factor for osteoporotic fractures [6,7]. Nevertheless there were two important consequences of this pivotal fracture trial with vitamin D/calcium supplements [5]: Pharmaceutical companies started to manufacture and sell Calcium-Vitamin D tablets and this supplementation advanced to a general basic therapy for all forms of osteoporosis.

In the following we will discuss the rationale to use vitamin D with or without calcium in osteoporosis and today's evidence in which clinical situations this supplementations can be effective in reducing the incidence of falls and fractures.

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Mode of action of vitamin D in osteoporosis

Early established effects of vitamin D (after conversion to D-hormone) were improvement of intestinal calcium absorption and mineralization of bone matrix. Accordingly high doses of vitamin D are able to heal the under-mineralisation in rickets and osteomalacia due to severe D-deficiency. In the mostly elderly patients with osteoporosis, however, a mild to moderate, chronic lack of vitamin D (often named as "D-insufficiency") leads to insufficient absorption of the mostly low amounts of ingested calcium and a consequent low normal serum calcium is followed by an increased PTH secretion of the parathyroid glands [8]. That means that in elderly patients with low vitamin D and calcium supply calcium homeostasis is kept at the expense of the skeleton. The developing moderate hyperparathyroidism ("senile hyperparathyroidism") induces bone loss and an increasing risk of fractures [9]. The proofs of this concept were studies showing that serum calcium concentrations could be elevated and PTH reduced by daily vitamin D and calcium supplementation [10].

Pathogenesis of fractures in osteoporosis

Parallel with increasing life expectancy and the worldwide growth of the older populations there is an important increase in the percentage of frail people with severe physical disability [11]. One important factor of the aging process is the loss of muscle mass and function leading to an increased risk of falling and fractures. The impairment of the central nervous system with a reduced balance contributes to the high risk of falling [12]. Since both sarcopenia and osteopenia are present in the majority of advanced age persons, the risk of suffering a fracture when falling is further augmented.

The most frequent localisations for osteoporotic fractures are the distal radius and ulna, the spine and the proximal femur. Less frequently fractures occur at the proximal humerus, pelvis, ankles, claviculae and ribs. It is important to note that taken together all non-vertebral fractures are more frequent than vertebral fractures in osteoporosis. While the latter may occur in part without falls or obvious trauma non-vertebral fractures are nearly always related to the traumatic impact of a fall [13].

In this context the important role of muscles and balance had long-time been neglected together with possible interactions of vitamin D. These interactions could have been suspected much earlier. Waddling gait due to proximal muscle weakness (Trendelenburg's sign) together with diffuse muscle pain were well known clinical symptoms of rickets or osteomalacia [14], i.e. of severe vitamin D deficiency. Figure 1 shows the osseous and muscular factors contributing to the risk and non-vertebral fractures
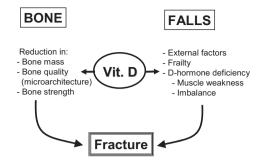

Figure 1. Pathogenetic factors contributing to non-vertebral fractures in osteoporosis and dual counteracting effects of vitamin D.

and vitamin D as a compound acting on both sides. In the meantime it is well established that muscle cells have vitamin D Receptors (VDRs) [15] and it was shown that the expression of these receptors in myocytes decreases significantly with age [16].

The evidence that vitamin D plays an important role in muscle health was supported by animal studies and trials in humans showing a positive association between 25(OH)D concentration, muscle strength and lower extremity function in the elderly [17,18].

The role of vitamin D in the therapeutic strategy of osteoporosis

The fact that the commonly used anti-osteoporotic drugs (bisphosphonates, raloxifen, strontium-ranelate, teriparatide, denosumab) aim only on a modification of bone turnover and not on the risk of falling, may explain that these drugs reduce primarily the incidence of new vertebral fractures and with less potency non-vertebral fractures where also falls play an important role. Only vitamin D, D-hormone itself or alfacalcidol, the prodrug of calcitriol have a dual effect on fractures and falls and thereby they should be able – alone or in combination with the above mentioned specific drugs – to act on the incidence of non-vertebral fractures [19]. This important chance led to the development of once weekly tablets with alendronate 70 mg plus 2,800 IU vitamin D [20] and later with 5,600 IU corresponding to 800 IU per week. There will be a fixed combination of strontium-ranelate plus 1,000 IU vitamin D for daily use in the near future. Improved compliance with vitamin D co-medication is regarded as the major advantage of these combinations.

While these are medications to treat established osteoporosis with prevalent fractures numerous studies and meta-analyses were published in the last two decades investigating the potency of plain vitamin D with or without calcium supplements to reduce falls and fractures in healthy or osteopenic populations.

Vitamin D and falls

The activated form of vitamin D appears to act on muscle tissue through its actions on the VDR, but the mechanisms involved have not been fully defined. There are also effects on balance but the underlying mechanisms are even less clear. It is presently generally accepted that an adequate vitamin D status is important to lower the risk of falling in older women and men and that circulating 25(OH)D concentrations of at least 60 nmol/L is needed to minimize the risk of falls.

The numerous trials investigating the incidence of fall reducing potency of native vitamin D resulted in part in very controversial results. In several studies with a long-term vitamin D and calcium supplementation clear positive effects on falls and parameters of muscle function could be shown in community dwelling older individuals [21–23]. In other randomised, controlled trials (RCTs) no significant effect on the risk of falling could be shown [24–27]. The inconsistent results between RCTs were analysed and discussed in numerous reviews. Possible explanations for no beneficial results were e.g. a too low daily dose of vitamin D, vitamin D given as an oral or parenteral bolus with long intervals, a poor compliance with dosage, or a low quality fall assessment. Indeed fall assessment may be challenging due to the fact that falls tend to be forgotten by elderly people if not associated with significant injury like a fracture [28].

Different meta-analyses with positive effects on the incidence of falls were published during the last decade based on increasing numbers of RCTs either analysing studies with plain vitamin D (cholecalciferol or ergocalciferol) or active vitamin D (calcitriol or alfacalcidol). A clear distinction between studies with plain or active vitamin D is mandatory because plain vitamin D will not be activated in vitamin D replete patients, or in elderly persons with an age related reduced creatinine clearance. In contrast calcitriol or the prodrug alfacalcidol act independent from the individual's vitamin D status and kidney function [29]. The selection of studies for incorporation into meta-analysis is always a critical issue. In one early meta-analysis on five trials including a total of 1,237 patients there was a significant 22 % reduction in falls [30]. A critical analysis, however, shows that this positive result was obviously driven by two studies having used calcitriol or alfacalcidol and making up one half of the total patients (n = 624). Another more recent meta-analysis involving eight trials and 2,426 individuals revealed that doses of vitamin D up to 600 IU were ineffective, whereas higher doses that ranged from 700 to 1,000 IU reduced risk of falling by about 20 % [31]. Obviously, the dosage of vitamin D supplements and the achieved plasma concentrations of 25(OH)D play an important role. An important confounding factor may be that some patients with initially very low 25(OH)D concentrations will take very long time to reach at least a concentration above 50 nmol/L. Again this study comprised trials with "supplemental" and "active" vitamin D [31]. The Institute of Medicine (IOM, Washington DC) published in the 2011 Report of Dietary Intakes for Calcium and Vitamin a very negative view. They concluded that "the greater part of the causal evidence indicated no significant reduction in fall risk related to vitamin D intake or achieved concentrations in blood [32].

We suggest that the controversial data on the potency of vitamin D to reduce falls are related to numerous interacting factors influencing the therapeutic response (Table I) and that by taking these factors into consideration individuals or populations could be identified who will have a beneficial effect on the risk of falling. Additional research is needed to confirm this view.

Vitamin D and fractures

As mentioned above vitamin D may act on the risk of fractures by a dual effect on bone and muscle strength (Figure 1). This possible dual benefit is especially attractive among elderly persons with a high risk of falls and non-vertebral fractures [33]. Non-vertebral fractures in advanced age are closely related to muscle weakness and falling. After a first fall about 30 % of elderly persons develop fear of falling [34]. This fear of falling may adversely affect bone density and muscle strength through restriction of physical activity [35].

The initially cited milestone study from Lyon 1992 [5] and a study from Boston, which appeared

Table I. Overview of factors that may influence the outcome of trials on reducing the risk of falls and fractures by vitamin D supplementation with or without calcium.

Related to medical intervention
  Dosage of vitamin D (400 IU insufficient, better 800 to 1000 IU)
  Additional calcium supplements (amount, calcium salt?)
  Compliance with prescription?
  Vitamin D status (25(OH)D concentration) at beginning of intervention
  Amount of regular dietary intake
  Other osteotropic drugs (e.g. estrogen, thiazides?)
Related to individual patients
  Age, fitness, physical activity, previous falls
  Individual living in community or institutionalized
  Other diseases e.g. Parkinson, polyneuropathy, rheum. disease
  Renal function (no or insuff. vit D activation with CrCl < 60 mL/min)
  Decrease in VDR-expression n muscle tissue with age
Related to study design
  Quality of fall assessment
  Measures to optimize patient adherence
  Follow up on 25(OH)D concentration, renal function

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5 years later [36] are still the most important ones proving a significant effect of plain vitamin D plus calcium on the incidence of fractures.

In a 5-year RCT on 2,686 subjects aged 65 to 85 years receiving 100,000 IU vitamin D every 4 months (equivalent to 833 IU/day) a 33 % fracture reduction could be proven [26] but disturbingly no significant effect on falls. In the huge Women's Health Initiative (WHI) seven year trial 36,282 post-menopausal women aged 50–79 (mean 62.4 yrs) received daily 400 IU vitamin D and 1,000 mg calcium [37]. The overall effect on fractures was not significant but in subgroups with an adherence > 80 % or an age > 60 years a significantly lowered risk of hip fractures was found. These results support our view discussed in the context of falls, that the selection criteria used for composing intervention groups plays an important role (see Table I).

A typical example of a very disappointing negative study is the RECORD Trial, performed in 21 UK hospitals [25]. 5,292 individuals, aged 70 years or older (85 % women), were randomized after a low trauma fracture to four intervention arms to receive daily 800 IU vitamin D, 1,000 mg calcium, both supplements or double placebo. The patients were followed up for between 24 and 62 months. The four groups did not differ in the incidence of all new fractures, hip fractures, death, number of falls, or quality of life [25].

Different studies with active vitamin D metabolites could demonstrate significant effects on osteoporosis related fractures [29]. Recently we investigated the effect of daily therapy with 1 μg alfacalcidol on muscle power, muscle function, balance performance and fear of falls in an open, uncontrolled, prospective study on a cohort of patients with reduced bone mass (n = 2,097). Participants underwent muscle function and muscle power tests at onset and after 3 and 6 months: the Timed Up and Go Test (TUG) and the Chair Rising Test (CRT).

A significant improvement in the performance of the two muscle tests was proven already after 3 months of treatment with alfacalcidol and further increased by the end of the therapeutic intervention. An increased fear of falling was reduced by the end of the study in 74.4 % of the patients. We suggest that the quantitative risk tests used in this study could be interesting surrogate parameters for the risk of falls and fractures in elderly patients.

Conclusion

A sufficient supply with vitamin D and calcium is important for normal development and maintenance of the skeleton. Vitamin D together with Ca is recommended as a basic therapy for all forms of osteoporosis, i.e. should be given together with any specific medication.

From the well established effects of vitamin D on calcium-phosphate metabolism and on muscle strength and function, beneficial effects on the risk of falls and non-vertebral fractures can be expected. Data, however, from different trials are not consistent due to criteria of patient selection (e.g. age, general health, renal function) and dosage of vitamin D and calcium, compliance and co-medication. The preventive effect on falls and fractures seems to be better in elderly, institutionalized, vitamin D/Ca-deficient people. A dosage of 800–1,000 IU of vitamin D seems to be superior to 400–600 IU. Furthermore, the elderly patients should be compliant with daily 800–1,000 IU vitamin D and 500–1,000 mg calcium and a high quality assessment of falls has to be adopted.

Questions and answers

P Lips, Netherlands

I have a question on the recommendations in respect of patients with some degree of renal failure, where using 0.5 to 1.0 μg of calcitrol might be too much?

JD Ringe

I was not talking about renal bone disease; I was speaking of osteoporosis in elderly patients with moderate renal function. When you treat renal bone disease you have to use higher doses to reduce the risk of secondary hyperparathyroidism but with a creatinine clearance of less than 60 mL/min there is reduced activation of plain vitamin D.

P Lips

In that group you might have a decrease in renal function by giving too much α-calcitrol. The usual recommendations are for a lower dose of calcitrol, 0.425 to 0.5 μg.

JD Ringe

When you give α-calcitrol you have to reduce the calcium supplements. Where there is a high intake of calcium in the diet, such as in your country through high dairy intake, then you need no calcium supplements with α-calcitrol because the intestinal absorption is very high.

JC Souberbielle, France

I had forgotten that in our study which you mentioned, calcium phosphate was used but at that time we did not know anything about FGF23. It is likely that if you give calcium phosphate you will increase the secretion of FGF23, which may have a worse effect on the hydroxylation of 25(OH)D3. What do you think?

JD Ringe

This has been looked at by Professor Heaney from Nebraska. He described studies which show that in elderly people there is not infrequently phosphate deficiency, sometimes due to too much calcium supplementation. If you give calcium carbonate, this binds phosphate from the diet in the gut, resulting in phosphate deficiency.

G Jones, Canada

In North America there is a definite movement towards giving both vitamin D and an active analogue. The theory is that these patients are vitamin D deficient and calcitrol deficient if their GFR falls too low and they end up with a compromised $1,25(OH)_2D3$ production. There is a movement afoot to introduce compounds to supplement vitamin D and give a small dose of the active analogue at the same time. I think the danger with giving $1\alpha(OH)D3$ is that we are only treating half the problem. The danger is that you are going to have $25(OH)D$ deficiency because of the effect of FGF23 on the drain of $25(OH)D$.

JD Ringe

In Europe too, for renal bone disease in patients on haemodialysis, it is not usual to give active vitamin D and plain vitamin D together but in osteoporosis this is an interesting approach. When considering treating individual patients or assessing them for inclusion in a study, it is essential to consider their renal function. If it is normal and the $25(OH)D$ is not very low, you can treat with plain vitamin D. However, if $25(OH)D$ is low you either have to give a loading dose of plain vitamin D or for a very rapid effect, you can give both plain and active vitamin D. This is what we do with patients who have 'osteomalacia of immigration' in dark-skinned people living in Europe, who have very low $25(OH)D$ concentrations. This has a rapid effect on muscle and bone and gives relief of pain in these patients.

G Jones

I agree that knowing the renal function is important but the stage of CKD is also important. One must be aware of the fact that there are other ways to replete besides just using plain vitamin D. $25(OH)D3$ preparations are being tested and are interesting. They could replete vitamin D deficiency faster and could be used in conjunction with the active analogue.

JD Ringe

Of course, we have all the non-renal activation sites to consider, which is another argument for this.

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