Optimal Use of Vitamin D When Treating Osteoporosis

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Abstract Inadequate serum 25-hydroxyvitamin D (25[OH] D) concentrations are associated with muscle weakness, decreased physical performance, and increased propensity in falls and fractures. This paper discusses several aspects with regard to vitamin D status and supplementation when treating patients with osteoporosis in relation to risks and prevention of falls and fractures. Based on evidence from literature, adequate supplementation with at least 700 IU of vitamin D, preferably cholecalciferol, is required for improving physical function and prevention of falls and fractures. Additional calcium supplementation may be considered when dietary calcium intake is below 700 mg/day. For optimal bone mineral density response in patients treated with antiresorptive or anabolic therapy, adequate vitamin D and calcium supplementation is also necessary. Monitoring of 25(OH)D levels during follow-up and adjustment of vitamin D supplementation should be considered to reach and maintain adequate serum 25(OH)D levels of at least 50 nmol/L, preferably greater than 75 nmol/L in all patients.

Keywords Vitamin D · Falls fractures · Supplementation · 25-hydroxyvitamin D (25[OH]D) · PTH · Neuromuscular function

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Introduction

Osteoporosis is a chronic, progressive disease characterized by reduced bone mass and microarchitectural deterioration of bone, involving an extensive fragility and a subsequent increase in fracture risk [1]. Fracture risk increases with age and is often associated with an increased bone remodeling resulting in bone resorption, loss of bone strength, and decrease of bone mineral density (BMD) [2]. More than 90% of fractures occur after a fall and fall rates increase with age postural instability and/or quadriceps weakness [3].

Inadequate serum 25-hydroxyvitamin D (25[OH]D) concentrations are associated with decreased intestinal calcium absorption causing compensatory increase in parathyroid hormone (PTH) levels and thus secondary hyperparathyroidism leading to a lower degree of mineral-
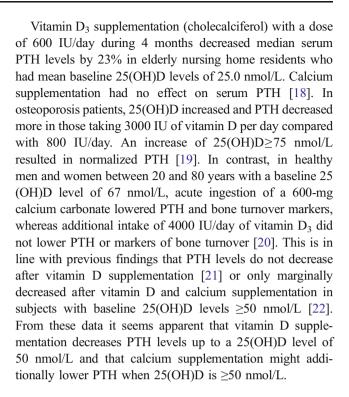
ization and accelerated bone loss [4, 5]. Declining vitamin D levels are also associated with muscle weakness, decreased balance and physical performance, and increased propensity in falls and fractures [6–8]. Vitamin D insufficiency has now been linked to a broad spectrum of human diseases from cancer to cardiovascular to autoimmune conditions, but these topics are out of the scope of this paper [9]. In this paper we discuss several aspects with regard to vitamin D status and supplementation when treating osteoporosis in relation to risks and prevention of falls and fractures based on a number of recently published meta-analyses.

Vitamin D Status

The stages of vitamin D deficiency are generally defined based on circulating 25(OH)D levels, in which a serum level less than 12.5 nmol/L is defined as severe deficiency, a level between 12.5 and 25 nmol/L as deficiency, and a level of 25 to 50 nmol/L as vitamin D insufficiency [5]. The 1,25-dihydroxyvitamin D assay should not be used for detecting vitamin D deficiency because levels will be normal or even elevated as a result of secondary hyperparathyroidism [10]. Several end points can be used for defining optimal vitamin D status in terms of 25(OH)D levels: prevention of PTH elevation, optimal muscle function, prevention of bone loss, falls or fractures.

Relationship Between 25(OH)D and PTH Levels and Vitamin D Supplementation

PTH is secreted in response to reduced calcium levels causing an increase in bone resorption and subsequently normalization of calcium levels. In case of vitamin D deficiency, secondary hyperparathyroidism results in increased bone turnover and bone loss and may subsequently increase fracture risk [5]. The relationship between 25(OH)D and PTH levels has been described in several cross-sectional studies, indicating a significant negative correlation between PTH and 25(OH)D values with only a minimal increase of PTH when serum 25(OH)D is above 50 to 75 nmol/L [11, 12, 13•, 14]. Recently, Carnevale et al. [14] demonstrated that PTH levels were mainly determined by 25(OH)D levels up to 40 nmol/L and to serum ionized calcium at levels greater than 40 nmol/L in healthy volunteers. In a recent study it has been shown that for the same 25-OHD level, PTH levels were comparable across genders but were 1.5- to twofold higher in the elderly compared with adolescents [15] and that elevated PTH is a strong independent predictor for poor outcomes in older patients [16, 17].

Vitamin D_3 supplementation (cholecalciferol) with a dose of 600 IU/day during 4 months decreased median serum PTH levels by 23% in elderly nursing home residents who had mean baseline 25(OH)D levels of 25.0 nmol/L. Calcium supplementation had no effect on serum PTH [18]. In osteoporosis patients, 25(OH)D increased and PTH decreased more in those taking 3000 IU of vitamin D per day compared with 800 IU/day. An increase of 25(OH)D≥75 nmol/L resulted in normalized PTH [19]. In contrast, in healthy men and women between 20 and 80 years with a baseline 25(OH)D level of 67 nmol/L, acute ingestion of a 600-mg calcium carbonate lowered PTH and bone turnover markers, whereas additional intake of 4000 IU/day of vitamin D_3 did not lower PTH or markers of bone turnover [20]. This is in line with previous findings that PTH levels do not decrease after vitamin D supplementation [21] or only marginally decreased after vitamin D and calcium supplementation in subjects with baseline 25(OH)D levels ≥50 nmol/L [22]. From these data it seems apparent that vitamin D supplementation decreases PTH levels up to a 25(OH)D level of 50 nmol/L and that calcium supplementation might additionally lower PTH when 25(OH)D is ≥50 nmol/L.

Relationship Between 25(OH)D Levels, Neuromuscular Function, and Vitamin D Supplementation

The nuclear receptor for vitamin D (VDR) is expressed in many human cell types, including muscle cells [10, 23]. Older age is associated with decreased VDR expression, independent of serum 25(OH)D levels [24]. The effect of vitamin D on muscle tissue is thought to occur through specific VDRs. Cross-sectional studies show that elderly people with deficient 25(OH)D serum levels have muscle weakness, particularly in proximal muscles, associated to a decrease in motion ability and capabilities, which increases the number of falls [25, 26]. A serum 25(OH)D level below 50 nmol/L is associated with increased body sway and a level below 30 nmol/L with decreased muscle strength [27]. In a prospective, population-based study, Visser et al. [28] showed that low 25(OH)D levels and high PTH levels increased the risk of sarcopenia in subjects 65 years of age or older. In both active and inactive ambulatory persons aged ≥60 years of age, 25(OH)D concentrations ≥40 nmol/L were associated with better musculoskeletal function in the lower extremities than concentrations less than 40 nmol/L [29] and in serum 25(OH)D concentrations below 50 nmol/L were associated with poorer physical performance and a greater decline in physical performance in men and women ≥65 years of age [7]. In randomized controlled trials (RCTs), vitamin D supplementation increased muscle strength and balance with 800 IU of vitamin D on top of calcium substitution [30, 31]. However, in a recent study by

Lips et al. [32], weekly treatment with 8400 IU of vitamin D did not reduce mediolateral sway significantly compared with treatment with placebo in subjects ≥70 years of age, with serum 25(OH)D levels between 15 and 50 nmol/L, although in post hoc analysis, treatment with 8400 IU of vitamin D per week reduced sway in the subgroup of patients who had elevated sway at baseline. Based on these results it seems likely that vitamin D substitution improves physical performance and that those with severe vitamin D deficiency experience the greatest benefit.

Relationship Between 25(OH)D Levels, Risk of Falling, and Vitamin D Supplementation

A beneficial effect of vitamin D supplementation on fall prevention among ambulatory or institutionalized older individuals with stable health by more than 20% was suggested by the meta-analysis of Bischoff-Ferrari et al. [33]. This meta-analysis was based on five RCTs involving 1237 participants treated with cholecalciferol or active vitamin D analogues compared with patients receiving calcium or placebo. The benefit was most clearly established for women and with active vitamin D analogues [33]. Active forms of vitamin D do not need hydroxylation in the kidney, so their effect on falls should be influenced less by age-related decline in kidney function than the effect of supplemental vitamin D. In 2008 one meta-analysis showed that active vitamin D supplementation seemed to prevent falls to a greater extent than their native compound [34] and in another small meta-analysis with combined data of two trials a significant risk reduction of falls was also demonstrated [35].

In a more recent meta-analysis the efficacy of vitamin D supplementation was assessed for the prevention of falls among older persons by dose and serum concentration of 25(OH)D achieved [36]. In this analysis 10 RCTS trials were included: three with ergocalciferol, five with cholecalciferol, and two with active forms of vitamin D doses (one with alfacalcidol and one with calcitriol). Dosages of supplemental vitamin D of 700 to 1000 IU/day could reduce falls by 19% or by up to 26% with ergocalciferol, independent of additional calcium supplementation. Vitamin D doses below 700 IU a day did not prevent falls. A 25(OH)D concentration of at least 60 nmol/L was required for fall prevention. From this analysis it seems likely that greater benefits may be achieved with vitamin D_3 instead of vitamin D_2. Active forms of vitamin D do not appear to be more effective than 700 to 1000 IU of vitamin D for fall prevention in this analysis [36].

In the Cochrane review of interventions for preventing falls in older people living in the community, the efficacy for fall prevention of supplementation with vitamin D or an analogue, either alone or with calcium co-supplementation, was analyzed [37]. The overall analysis of vitamin D versus control did not show a statistically significant difference in rate of falls or risk of falling in 10 studies with 21,110 participants. In a post hoc subgroup analysis the rate of falls was significantly reduced in trials recruiting participants with lower (<50 nmol/L) baseline 25(OH)D levels (relative risk [RR], 0.57; 95% CI, 0.37–0.89 in 260 participants, two trials) but not in participants not so selected (RR, 1.02; 95% CI, 0.88–1.19 in 3669 participants, three trials). For calcitriol but not alfacalcidol a significant reduction in rate of falls and risk of falling was reported; however, there was also a significant increase in the risk of hypercalcemia [37].

The Cochrane review of interventions for preventing falls in older people in nursing care facilities and hospitals reported a significant reduction of the rate of falls (RR, 0.72; 95% CI, 0.55–0.95, 4512 participants in four trials; one with cholecalciferol and three with ergocalciferol), although the number of fallers was not significantly different (RR, 0.98; 95% CI, 0.89–1.09, 5095 participants in five trials; two with cholecalciferol and three with ergocalciferol) with vitamin D supplementation compared with placebo or calcium in nursing care facilities [38]. Average serum 25(OH)D levels were between 22 and 47 nmol/L in the included studies. Caution may be required with interpretation of these pooled data because of statistical and clinical heterogeneity.

In the most recent review including 10 RCTs, vitamin D treatment effectively reduced the risk of falls with 14% in community dwelling and institutionalized older adults with a mean age from 71 to 92 years [39]. Three types of vitamin D (six studies with cholecalciferol, three with ergocalciferol, and one with alfacalcidol) were used. In seven studies patients used additional calcium therapy and in three studies no additional medication was used. Treatment duration ranged between 1 and 36 months, and native vitamin D dosage ranged between 200 and 1000 IU. The effect of vitamin D on fall reduction was significant in several subgroups of individuals: mean age younger than 80 years, additional calcium therapy, no history of fracture or fall, dose of 800 IU or greater, cholecalciferol therapy, duration of treatment longer than 6 months, although no evidence was found of a relationship between higher doses of vitamin D or longer duration of vitamin D therapy and treatment effect [39]. It has to be noted that all studies included in the meta-analysis had populations with 25(OH)D levels less than 75 nmol/L.

Relationship Between 25(OH)D Levels, Risk of Fractures, and Vitamin D Supplementation

During the past years several meta-analysis have been published on the effect of vitamin D with and without

calcium with fracture incidence as outcome criterion [40–42, 43••, 44••, 45, 46••]. The analysis of Bischoff-Ferrari et al. [40], including five RCTs for hip fracture (n=9294) and seven RCTs for nonvertebral fracture risk (n=9820), concluded that vitamin D dose of 700 to 800 IU/day reduced the relative risk of hip fracture by 26% (three RCTs with 5572 persons; pooled RR, 0.74; 95% CI, 0.61–0.88) and of any nonvertebral fracture by 23% (five RCTs with 6098 persons; pooled RR, 0.77; 95% CI, 0.68–0.87) versus calcium or placebo in individuals ≥60 years of age. No significant benefit was observed for RCTs with 400 IU/day of vitamin D (two RCTs with 3722 persons) [40]. The meta-analysis by Boonen et al. [41], designed to extend the findings of Bischoff-Ferrari et al. [40], suggested that only vitamin D with additional calcium demonstrated a significant reduction of hip and nonvertebral fractures versus placebo or no treatment. A total of 53,260 patients from nine RCTs were included in this analysis and all RCTs used cholecalciferol with a dose of 700 to 800 IU/day in six trials and 400 IU/day in the other three trials. Calcium (500–1200 mg/d) was given with vitamin D in six RCTs. In an adjusted indirect comparison further support was found for combined supplementation of vitamin D and calcium, with a 25% reduction in hip fracture risk compared with vitamin D alone and it was suggested that oral vitamin D appears to reduce the risk of hip fractures only when calcium supplementation is added [41]. It has to be noted that two trials with very low nutritional baseline calcium intake had an important impact on the results of this meta-analysis [47, 48].

The meta-analysis of Tang et al. [42] showed that calcium supplementation, alone or in combination with vitamin D, was effective in the preventive treatment of osteoporotic fracture. The fracture risk reduction was greater in individuals who were elderly, living in institutions, and had a low baseline calcium intake. Treatment was similarly effective whether persons used calcium or calcium in combination with vitamin D supplementation. However, the treatment was less effective if compliance was lower than 80%. For calcium-only supplementation, a minimum dose of 1200 mg was needed for best therapeutic effect. For calcium in combination with vitamin D supplementation, a minimum dose of 800 IU of vitamin D was recommended. There was no significant difference in fracture reduction between low versus normal 25(OH)D serum concentration at baseline [42].

In the more recent analysis by Bischoff-Ferrari [43••], which included 12 RCTs for nonvertebral fractures (two with ergocalciferol, 10 with cholecalciferol; n=42,279) and eight RCTs for hip fractures (n=40,886) in individuals 65 years or older, the antifracture efficacy of supplemental vitamin D increased significantly with higher received dose or higher achieved 25(OH)D levels (>75 nmol/L) for any nonvertebral fractures and for hip fractures. No fracture reduction was observed for a dose of 400 IU/day or less,

whereas a higher dose of 482 to 770 IU/day of supplemental vitamin D reduced nonvertebral fractures by 20% and hip fractures by 18%. Subgroup analyses for the prevention of nonvertebral fractures with the higher received dose suggested possibly better fracture reduction with cholecalciferol compared with ergocalciferol, whereas additional calcium did not further improve antifracture efficacy [43••]. The analysis by Bergman et al. [45] supports the use of cholecalciferol 800 IU daily to reduce the incidence of osteoporotic nonvertebral, hip, and nonvertebral–non-hip fractures in women over 50 years of age. In this study, cholecalciferol with calcium appears to achieve benefits above those attained with calcium supplementation alone for nonvertebral and nonvertebral–non-hip fractures [45].

The Cochrane meta-analysis suggested that vitamin D alone appeared unlikely to be effective in preventing hip fracture (nine trials, 24,749 participants; RR, 1.15; 95% CI, 0.99–1.33), vertebral fracture (five trials, 9138 participants; RR, 0.90; 95% CI, 0.42–1.92), or any new fracture (10 trials, 25,016 participants; RR, 1.01; 95% CI, 0.93–1.09). Vitamin D with calcium reduced hip fractures (eight trials, 46,658 participants; RR, 0.84; 95% CI, 0.73–0.96) [44••].

In the most recent meta-analysis by the DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) group, seven major randomized trials of vitamin D with calcium or vitamin D alone, with a total of 68,517 participants (mean age 69.9 years; range 47–107 years; 14.7% men) were included [46••]. In this analysis based on individual patient data analysis it was also indicated that vitamin D with calcium showed a reduced overall risk of fracture (hazard ratio [HR], 0.92; 95% CI, 0.86–0.99; P= 0.025) and hip fracture (all studies: 0.84, 0.70–1.01; P= 0.07; studies using 400 IU of vitamin D per day given with calcium: 0.74, 0.60–0.91; P=0.005). Vitamin D given alone in doses of 400 to 800 IU per day was not effective in preventing fractures [46••].

Supplementation with high-dose vitamin D supplementation annually could be harmful. Among 2256 older community-dwelling women, annual oral administration of 500,000 IU of cholecalciferol resulted in an increased risk of falls and fractures compared with placebo [49•]. An annual intramuscular injection of 300,000 IU of ergocalciferol was not effective in preventing nonvertebral fractures among 9440 elderly men and women residents in the general population. The HR for hip fracture was significantly increased (HR, 1.49; 95% CI, 1.02–2.18) [50].

Optimal Vitamin D Dose for Reduction of Falls and Fractures

It seems likely that vitamin D substitution improves physical performance and that elderly and those with severe

vitamin D deficiency experience the greatest benefit. Based on evidence from RCTs and the meta-analyses, vitamin D supplementation reduces both falls and fractures. The beneficial effect of vitamin D is dose dependent and mainly demonstrated for cholecalciferol with a dose of at least 700 IU/day. Active vitamin D is not preferred because of the increased risk of hypercalcemia.

Annually high-dose vitamin D supplementation could possibly increase fall and fracture risk. It was suggested that a 25(OH)D concentration of at least 60 nmol/L was required for fall prevention and optimal fracture prevention appeared to occur in trials with achieved mean 25(OH)D levels of approximately 75 to 100 nmol/L. Additionally, adequate 25(OH)D levels were required for an optimal BMD response in patients who are being treated with bisphosphonates for osteoporosis [51], and coadministration of cholecalciferol and calcium vitamin D with antiresorptive medication improved the subsequent BMD response unaffected by vitamin D status at initiation [52, 53]. However, the practical clinical question is whether all treated patients will receive a 25(OH)D level greater than 60 nmol/L with a vitamin D dose of 700 or 800 IU/day and if not, what vitamin D intake is needed to achieve serum concentrations greater than 60 nmol/L. It has been reported that the rate of increase of 25(OH)D levels was between 0.6 and 1.2 nmol/L per 40 IU daily of vitamin D_3 and that the response may well be an inverse function of the starting 25(OH)D concentration [54]. Seasonal fluctuations on 25(OH)D levels may further contribute to insufficient vitamin D status during winter months, especially in the elderly [55]. Based on these aspects it seems warranted to measure a baseline 25(OH)D level in all patients who are going to be treated with antiosteoporosis medication such as patients with a fracture or low bone mass, and to monitor 25(OH)D levels during follow-up and to adjust vitamin D supplementation when desired 25(OH)D levels are not achieved. In patients with severe vitamin D deficiency supplementation may be started with cholecalciferol 20,000 to 50,000 IU/week orally for 3 months until 25(OH)D levels are at least 50 nmol/L, followed by a daily dose of at least 700 IU. Higher dosages may be necessary when desired 25(OH)D levels are not maintained [19, 56].

In addition to vitamin D status, calcium balance must be optimized. For persons older than 50 years, a total calcium intake of 1000 to 1200 mg per day was advised [57]. Calcium supplementation may be needed when dietary calcium intake is insufficient, although a calcium intake greater than 700 mg/day may be only beneficial for better BMD when 25(OH)D levels are less than 50 nmol/L [58•]. The meta-analysis by Bischoff-Ferrari et al. [59] showed no reduction in hip fracture risk with calcium supplementation. In addition, recent publications suggest an increased risk of myocardial infarction with calcium supplementation with-out coadministration of vitamin D [60]. However, the risk of myocardial infarction was not increased in people with dietary calcium intake below a median dietary calcium intake of 805 mg/day [60]. Thus, calcium supplementation may be considered when dietary calcium intake is below 700 mg/day, with a calcium supplementation dose that leads to a maximum total daily calcium intake of 1000 to 1200 mg.

Conclusions

Poor vitamin D status and low calcium intake are important determinates for osteoporosis and fracture risk. Based on evidence from literature, adequate supplementation with at least 700 IU of vitamin D, preferably cholecalciferol, is required for improving physical function and prevention of falls and fractures. Additional calcium supplementation may be considered when dietary calcium intake is below 700 mg/day, with a supplementation dose that leads to a maximum total daily calcium intake of 1000 to 1200 mg. For optimal BMD response in patients treated with antiresorptive or anabolic therapy, adequate vitamin D and calcium supplementation is also necessary. It should be considered to monitor 25(OH)D levels during follow-up of patients with osteoporosis to warrant adequate vitamin D status during treatment and if necessary adjust the vitamin D supplementation dose to reach or maintain 25(OH)D levels of at least 50 nmol/L, preferably greater than 75 nmol/L in all patients.

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