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REVIEW ARTICLE

Reducing fracture risk with calcium and vitamin D

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Summary

Studies of vitamin D and calcium for fracture prevention have produced inconsistent results, as a result of different vitamin D status and calcium intake at baseline, different doses and poor to adequate compliance. This study tries to define the types of patients, both at risk of osteoporosis and with established disease, who may benefit from calcium and vitamin D supplementation. The importance of adequate compliance in these individuals is also discussed. Calcium and vitamin D therapy has been recommended for older persons, either frail and institutionalized or independent, with key risk factors including decreased bone mineral density (BMD), osteoporotic fractures, increased bone remodelling as a result of secondary hyperparathyroidism and increased propensity to falls. In addition, treatment of osteoporosis with a bisphosphonate was less effective in patients with vitamin D deficiency. Calcium and vitamin D supplementation is a key component of prevention and treatment of osteoporosis unless calcium intake and vitamin D status are optimal. For primary disease prevention, supplementation should be targeted to those with dietary insufficiencies. Several serum 25-hydroxyvitamin D (25(OH)D) cut-offs have been proposed to define vitamin D insufficiency (as opposed to adequate vitamin D status), ranging from 30 to 100 nmol/l. Based on the relationship between serum 25(OH)D, BMD, bone turnover, lower extremity function and falls, we suggest that 50 nmol/l is the appropriate serum 25(OH)D threshold to define vitamin D insufficiency. Supplementation should therefore generally aim to increase 25(OH)D levels within the 50–75 nmol/l range. This level can be achieved with a dose of 800 IU/day vitamin D, the dose that was used in succesfull fracture prevention studies to date; a randomized clinical trial assessing whether higher vitamin D doses achieve a greater reduction of fracture incidence would be of considerable interest. As calcium balance is not only affected by vitamin D status but also by calcium intake, recommendations for adequate calcium intake should also be met. The findings of community-based clinical trials with vitamin D and calcium supplementation in which compliance was moderate or less have often been negative, whereas studies in institutionalized patients in whom medication administration was supervised ensuring adequate compliance demonstrated significant benefits.

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Introduction

Osteoporotic fractures are a growing health care problem, with an estimated lifetime risk for 50-year-old Caucasians of at least 40% for women and 13% for men.[1] Osteoporotic fractures occur most frequently in the spine and hip, but may also affect the pelvis, wrist and upper arm. Vertebral as well as nonvertebral fractures can cause serious morbidity, including chronic pain and disability,[2] increased dependence and potentially institutionalization;[3] both types of fracture are also associated with excess mortality.[3–5] Fracture risk increases exponentially with age and with the decrease in bone mineral density (BMD), often associated with an increased rate of bone remodelling, resulting in net bone resorption and a consequent reduction in bone strength.[6] Another cause is the increase in fall incidence with ageing.[7] The main determinants of the age-related increase in bone turnover are declining estrogen levels, changes in calcium and vitamin D metabolism and decreasing physical activity.[8,9] Calcium is important for bone health throughout life.[10] Vitamin D status is a determinant of the intestinal absorption of calcium and is therefore essential for maintaining calcium homeostasis.[10] The elderly are at risk of vitamin D deficiency and insufficiency, because of their reduced mobility and consequent decreased exposure to sunshine.[11] The capacity of the skin to synthesize vitamin D also decreases with age. In the presence of inadequate vitamin D status, calcium absorption is lower than optimal and there is a compensatory increase in parathyroid hormone (PTH) levels (secondary hyperparathyroidism), with a consequent stimulation of bone resorption and accelerated bone

loss.[11,12] The high bone turnover associated with elevated PTH levels is characterized by a lower degree of mineralization.[11,12] Vitamin D also plays an important role in maintaining muscular strength.[13] Declining vitamin D levels in older individuals are associated with muscular weakness, decreased physical performance when serum 25(OH)D is lower than 50 nmol/l[14] and an increased propensity to falls and fractures, when serum 25(OH)D is lower than 25–30 nmol/l.[15,16] A fall is implicated in many fractures, including those of the wrist, humerus and hip.[7]

The contribution of declining calcium and vitamin D levels to the pathophysiology of osteoporotic fractures provides a rationale for combined supplementation in at-risk individuals. The efficacy of antiresorptive therapies for osteoporosis appears to be less in the presence of low calcium intake and vitamin D deficiency, as was shown in an Italian and a Japanese study.[17,18] On the contrary, a study in the US did not show additional benefit of a calcium supplement of 1000 mg/day in alendronate-treated women with postmenopausal osteoporosis with a baseline calcium intake of ≥800 mg/day and vitamin D 400 IU/day,[19] indicating that large supplements are not necessary when baseline intake is adequate. The general consensus is that antiresorptive and anabolic therapies should be supplemented with both calcium and vitamin D unless the clinician is confident that calcium intake is adequate and vitamin D status is optimal.[20] Calcium and vitamin D supplementation in institutionalized elderly individuals with poor nutritional status, can suppress secondary hyperparathyroidism, reduce bone resorption, increase BMD and reduce fracture risk.[21] Supplementation with vitamin D with or without calcium may aditionally reduce the risk of falls in the elderly.[15,22] However, not all studies of calcium and vitamin D supplementation in the elderly have demonstrated benefits in terms of fracture reduction. This study explores these issues and identifies cut-offs for intervention, in terms of calcium intake and vitamin D status, above which universal benefit in terms of fracture prevention is likely to be negligible.

Defining optimal calcium intake

According to the US National Academy of Sciences, 1200 mg/day is an adequate intake of calcium for men and women aged over 50 years, whereas 1000 mg/day is sufficient for younger adults.[23] Guideline recommendations in Europe are lower, for example, 800 mg/day for women aged 50–65 years.[24] Many apparently healthy adults have calcium intakes below both benchmarks:[25,26] for example, in a normal adult population (aged 35–65 years) resident in France (n = 1579) mean intake of calcium was 849 mg/day.[25] The elderly, both those living in the community as well as institutions, often have poorer diets and are more likely to have insufficient dietary calcium intakes. Indeed, mean calcium intake in a cohort of elderly community-dwelling French women (75–90 years) was 569 mg/day.[27] Patients with documented osteoporosis generally also have an inadequate dietary calcium intake. A review of baseline data from six of the major osteoporosis trials revealed that 85% of participants had calcium intakes <1200 mg at study entry, with a mean of 727 mg/day,[28] that is, >50% of participants did not achieve the European recommended calcium intake of 800 mg/day.

Nevertheless, definition of the optimal calcium intake is hampered by several uncertainties. People in Africa and Asia survive with low to very low calcium intakes.[29] A study in Iceland suggested that a calcium intake >800 mg/day is not necessary for preventing an increase of serum PTH when serum 25(OH)D > 25 nmol/l.[30] A recent meta-analysis of prospective cohort studies and clinical trials did not show a decreased fracture risk with a high *vs.* low calcium intake.[31] A recent trial in New Zealand with a calcium supplement of 1000 mg/day showed an increase in combined cardiovascular end-points compared with the placebogroup.[32] In the Women's Health Initiative, a trial in 36,282 women with calcium 1000 mg/day and vitamin D 400 IU/day *vs.* double placebo, the incidence of kidney stones increased with 17%.[33] One can conclude that the calcium requirement cannot be exactly defined. Low intakes may cause secondary hyperparathyroidism, while high intakes carry a risk of side effects. A total intake from diet and supplements of about 1000 mg/d probably is sufficient and safe.

Defining optimal vitamin D status

Circulating 25(OH)D levels indicative of a deficiency state is typically defined as <25 nmol/l (Table 1).[11] It has become apparent, however, that PTH-induced bone loss continues to occur above this threshold.

A number of biochemical or clinical end-points can be used to establish the 25(OH)D threshold that defines optimal vitamin D status: suppression of circulating PTH; prevention of high bone turnover; prevention of bone loss and obtaining optimal BMD; optimal physical performance; prevention of falls; and prevention of fractures. Based on these, a number of different 25(OH)D thresholds have been proposed: 30, 50 and 75 nmol/l (Table 1).[11,34,35] These divergent viewpoints may be explained by the use of different 25(OH)D assays,[11,36] the fact that the PTH levels associated with vitamin D insufficiency (as opposed to the deficiency state) tend to remain within the normal reference range,[37] and the confounding effect of the variation in calcium intake between studies. Magnesium deficiency and decreased renal function also cause an increase of serum PTH.[38,39] The relationship between 25(OH)D and PTH levels in a normal adult population (n = 1569; aged 35–65 years, mean serum 25(OH)D of 61·2 nmol/l) has been described by Chapuy and colleagues.[25] A significant negative correlation was found between PTH and 25(OH)D values

Table 1. Stages of vitamin D deficiency

Stage	Serum 25(OH)D* (nmol/l)	Serum 25(OH)D* (ng/ml)	Increase in PTH (%)
Vitamin D insufficiency	25–50†	<10–20†	15
Vitamin D deficiency	<25	<10	15–30
Severe vitamin D deficiency	<12·5	<5	>30

25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.
*Determined by radioimmunoassay.
†Range of values proposed (see text).

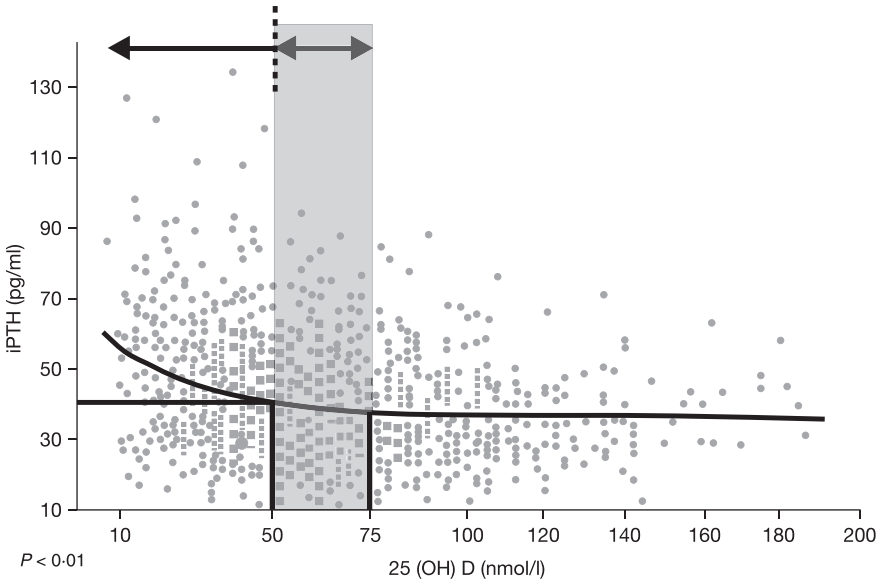

Fig. 1 Relationship between serum 25-hydroxy-vitamin D (25[OH]D) and serum intact parathyroid hormone (PTH) (adapted from Ref. 25, © 1997, The Endocrine Society). The shading has been added to highlight the 25(OH)D range of interest, that is, between 50 and 75 nmol/l.

($P < 0{\cdot}01$), with the curve reaching a plateau when serum 25(OH)D reached 78 nmol/l (Fig. 1). The increase of serum PTH was minimal between the 50 and 75 nmol/l 25(OH)D cut-off points, suggesting that 50 nmol/l may be a more appropriate threshold to define vitamin D insufficiency than 75 nmol/l. A similar relationship between serum 25(OH)D and PTH levels was observed in other studies,[37,40] one of these, the Longitudinal Aging Study Amsterdam, showing a decrease of serum PTH until serum 25(OH)D was above 100 nmol/l.[40] In that study, however, the bone turnover markers serum osteocalcin and urinary deoxypyridinolin started to increase when serum 25(OH)D was lower than 40 nmol/l (Fig. 2).

The relationship between PTH and 25(OH)D levels has also been explored in studies of calcium and high-dose vitamin D supplementation. In one study, after 8 weeks' supplementation, PTH levels fell by 35% in subjects with baseline 25(OH)D levels of 27·5–39·9 nmol/l, by 26% in those with levels of 40–49·9 nmol/l but showed no significant change in subjects with baseline 25(OH)D levels ≥50 nmol/l, despite a 66% increase in their serum 25(OH)D levels on treatment.[34] In the placebo group of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial,[41] in which both treatment arms received calcium (500–600 mg/day) and vitamin D (400–600 IU/day) supplements, serum PTH levels showed little change at 6 months (–0·2 pmol/l, –5%) in women with baseline 25(OH)D levels >50 nmol/l compared with those with baseline levels below this threshold (–0·8 and –0·5 pmol/l, or –22% and –14%) in patients with baseline serum 25(OH)D levels <25 and 25–50 nmol/l, respectively. The small increase in serum PTH when serum 25(OH)D decreases from 75 to 50 nmol/l may be considered physiological. In analogy, while a negative relationship exists between serum TSH and T4 most clinicians would not treat a hypothyroid patient by suppressing serum TSH below the reference range.

The relationship between lower extremity function and serum 25(OH)D levels has been examined in the NHANES III study (Fig. 3);[42] in this population of ambulatory older adults ($n = 4100$; aged ≥60 years) there was a sharp functional decline in the walk test and chair stand test when levels fell below 50 nmol/l. Physical performance, consisting of five chair stands, 3-m walking test and tandem stand, was studied in the Longitudinal Aging Study Amsterdam (LASA) in relation to serum 25(OH)D. Physical performance improved with increasing 25(OH)D up to 50 nmol/l after appropriate adjustment for age.[14] In LASA, fall incidence was related to vitamin D status, with an increased risk in individuals with serum 25(OH)D levels below 25 nmol/l.[15] In the same study, fracture risk was increased in older persons aged 65–75 years with serum 25(OH)D < 30 nmol/l compared with those with serum 25(OH)D > 30 nmol/l.[16] With respect to fall prevention, the most adequately designed study of vitamin D supplementation,[43] in which calcium supplements were given in both treatment arms, provides good evidence of efficacy of vitamin D in patients with a baseline 25(OH)D level < 50 nmol/l, as nearly all participants had a baseline level below this threshold (range: 23–55 nmol/l); the reduction in risk of falls associated with vitamin D therapy (800 IU/day) was 49% over a 3-month period. Based on the evidence presented above, we suggest that 25(OH)D levels < 50 nmol/l are indicative of insufficiency and require supplementation. A high proportion of individuals with restricted mobility and/or living in institutions are vitamin D insufficient by this criterion.[15,27] Data also indicate that a substantial proportion of patients with established osteoporosis do not have optimal vitamin D status.[37,41,44] The target serum 25(OH)D level of 50 nmol/l should be achievable with a vitamin D dose of 800 IU/day, the highest dose that has been evaluated to date in randomized clinical trials with fracture as outcome, such as Decalyos I and Decalyos II.[21,45]

Clinical trials of vitamin D and calcium with fracture as outcome criterion

During the last 20 years at least 14 randomized clinical trials (RCT) have been performed on the effect of vitamin D with or without

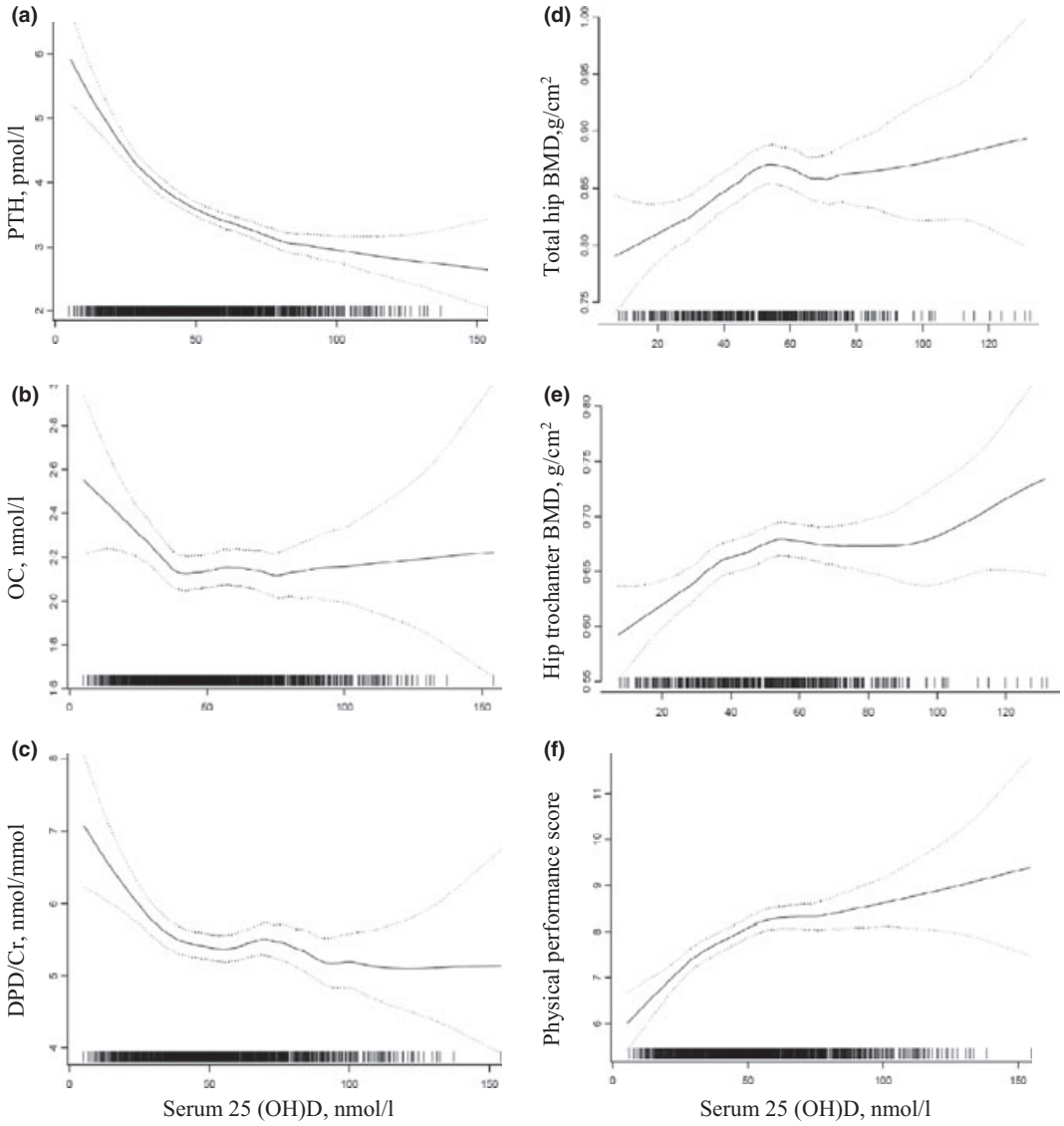

Fig. 2 Relationship between serum 25(OH)D and serum PTH, serum osteocalcin (OC), urine deoxypyridinoline/creatinine (DPD/Cr), BMD in total hip and trochanter and physical performance score. Data are from 1319 men and women ≥65 years in the Longitudinal Aging Study Amsterdam. Data are shown as locally weighted regression smoothing (LOESS) plots (adapted from Ref. 40). Figure 2 significance: serum 25(OH)D with PTH (A) P<0.001, osteocalcin (OC) (B) P=0.13, deoxypyridinoline/creatinine (C) P=0.006, BMD of total hip (D) P=0.15, BMD of femoral trochanter (E) P=0.10, and physical performance (F) P= 0.002. Reproduced with permission by the Endocrine Society.

calcium with fracture incidence as outcome criterion.[21,33,45–56] Four of these trials showed a significant reduction of fracture incidence, two were borderline while the eight other studies did not show a significant effect on fracture incidence (Table 2). Three of the negative studies showed a significant decrease of fall incidence.[51,54,56] In general, trials using vitamin D 800 IU/day tended to be more positive than trials using lower doses. Concerning calcium supplements, it is difficult to draw definite conclusions. The very successful French trials (Decalyos I and II) used vitamin D 800 IU/day and calcium 1200 mg/day *vs.* double placebo.[21,45] They were performed in a nursing home setting and patients were vitamin D deficient, had very low baseline calcium intake and compliance was ensured by the nurses. Community-based trials such as the Record trial, a well-designed factorial trial, were less successful.[52] Within the Women's Health Initiative, a very large double blind trial with calcium 1000 mg/day and vitamin D3 400 IU/day *vs.* placebo was conducted,[33] but the effect on hip fracture incidence was not significant (RR: 0·88, 95% CI: 0·72–1·08). This may be due to relatively high baseline serum 25(OH)D (48 nmol/l), the low vitamin D dose of 400 IU, or moderate compliance. The per-protocol analysis including only those participants who took >80% of the medication showed a significant decrease of hip fracture incidence (RR: 0·71, 95% CI: 0·52–0·97). Two trials were performed with vitamin D 100,000 IU/4 months *vs.* placebo,[49,55] the first showing a significant reduction of nonvertebral fractures, the other showing no effect. In the latter trial, serum 25(OH)D showed an

Table 2. Results of randomized clinical trials of vitamin D and calcium with fracture as outcome criterion

Reference	Patients	Vitamin D dose	Calcium dose mg/day	Obtained 25(OH)Dnmol/l	PTH decrease	BMD increase	Fracture risk reduction
21	3270	800 IU/day	1200	71	−44%	+6%	Hip:−43%*, nonvert:−32%*
46	2578	400 IU/day		54	−15% (Ref. 57)	+2·2%	Hip: NS, nonvert: NS
47	389	700 IU/day	500	99	−15%	+1%	Nonvert: $P - 50\%$*
45	583	800 IU/day	1200	80	−40%	+5%	Nonvert: $P = 0{\cdot}07$
48	569	400 IU/day					Hip: NS, nonvert: NS
49	2686	100,000 IU/4 months		74	−6%		Nonvert: −22%*
50	9605	400 IU/day	1000	47	−15%		Nonvert: −16%*
51	150	800 IU/day	1000	52	−30%	+3%	Nonvert: NS, falls −52%*
52	5292	800 IU/day	1000	62	−20%		Hip:NS, nonvert: NS
53	3454	800 IU/day	1000				Hip:NS, nonvert: NS
33	36,282	400 IU/day	1000			+1%	hip:NS, total fr: NS (hip:per protocol: −29%*)
54	625	1000 IU/day	600				Nonvert:NS, falls:−27%*
55	3440	100,000 IU/4 months		80	−25%		Nonvert:NS
56	242	800 IU/day	1000	84	−20%		Nonvert:NS, falls:−27%*

Hip, hip fracture; nonvert, nonvertebral fracture; NS, not significant.
*$P < 0{\cdot}05$.

adequate increase and serum PTH decreased about 25%. These divergent results are difficult to explain.

Five meta-analyses have been performed.[58–62] The meta-analysis of Bisschoff-Ferrari and colleagues concluded that vitamin D 800 IU/day is better than 400 IU/day.[58] The Cochrane meta-analysis suggested that trials in institutionalized patients are more successful than community-based trials, which may be explained by better compliance.[59] Boonen and colleagues performed a meta-analysis of RCTs of oral vitamin D with or without calcium supplementation *vs.* placebo/no treatment in older individuals.[60] Based on four RCTs (9083 patients), the pooled RR of hip fracture for vitamin D alone was 1·10 (95% CI: 0·89–1·36). For the 6 RCTs (45,509 patients) of vitamin D with calcium supplementation, the pooled RR for hip fracture was 0·82 (95% CI 0·71–0·94), suggesting that oral vitamin D appears to reduce the risk of hip fractures only when calcium supplementation is added. In an adjusted indirect comparison of the summary RRs from the two meta-analyses, the RR for hip fracture for vitamin D with calcium *vs.* vitamin D alone was 0·75 (95% CI: 0·58–0·96). Thus, to optimize clinical efficacy, vitamin D 700–800 IU/d should be complemented with calcium, using a dose of 1000–1200 mg/day of elemental calcium. However, the two French trials (Decalyos I and II)[21,45] with very low baseline calcium intake have a major impact in this meta-analysis. The meta-analysis of Tang and colleagues includes a sensitivity analysis, showing that trials were more successful when performed in institutions than in the community, when baseline calcium intake was low *vs.* high, when using vitamin D doses of 800 IU/day or more than lower doses, and when compliance was higher than 80% *vs.* lower compliance.[61] The recent meta-analysis of Bischoff-Ferrari and colleagues[62] on 12 randomized controlled trials showed a RR of 0·86 (95% CI: 0·77–0·96) for nonvertebral fractures and on eight RCTs a RR of 0·91 (95% CI 0·78–1·05) for hip fractures. Pooling five trials with a vitamin D dose higher than 400 IU/day, the RR for hip fractures was 0·82 (95% CI: 0·69–0·97). This confirms that the optimal dose probably is 800 IU/day and that compliance is of crucial importance. An additional benefit is the decrease in fall incidence.[51,54,56] Calcium supplementation is particularly important when baseline calcium intake is low.

In conclusion, vitamin D and calcium supplementation are most effective in housebound or institutionalized elderly who are vitamin D deficient and have a low dairy intake.

Compliance with calcium and vitamin D therapy

The mixed outcomes of the fracture studies with calcium and vitamin D supplementation in the community setting also highlight the importance of compliance. Compliance and persistence with medication in chronic diseases including osteoporosis is frequently less than optimal[63] and this may dilute the treatment effect. As outlined above, randomized clinical trials of calcium and vitamin D in institutionalized women, in whom medication administration is supervised, have shown positive benefits in terms of fracture reduction.[21,45] In contrast, in two negative community-based fracture prevention trials much lower levels of compliance with calcium and vitamin D, between 40% and 60%, were reported.[52,53] In addition, selective noncompliance could play a role: the frail elderly have a greater need of vitamin D supplements but are less likely to be compliant, unless institutionalized. Low serum 25(OH)D is an important frailty marker.[64]

The need to maintain long-term therapy with calcium and vitamin D supplements is supported by a study that followed patients (aged ≥68 years) who had completed a 3-year placebo-controlled trial of calcium and vitamin D for 2 years after discontinuation of the trial medication.[65] The improvements in BMD that had occurred at the femoral neck and the lumbar vertebrae during supplementation were largely reversed 2 years after treatment withdrawal in both men and women (Fig. 4); the reduction in bone

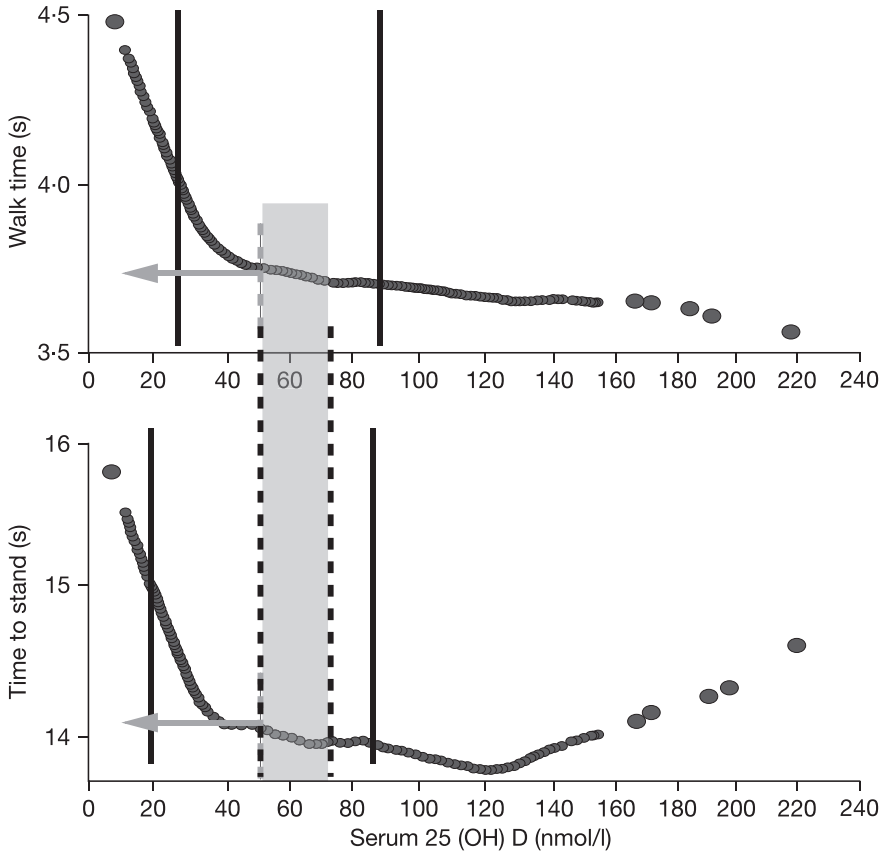

Fig. 3 Association between 25(OH)D levels and lower extremity function in an ambulatory elderly population aged over 60 years (n = 4100) (adapted from Ref. 42). The shading has been added to highlight the 25(OH)D range of interest, that is, between 50 and 75 nmol/l. Reproduced with permission by the American Journal of Clinical Nutrition. © Am J Clin Nutr. American Society for Clinical Nutrition.

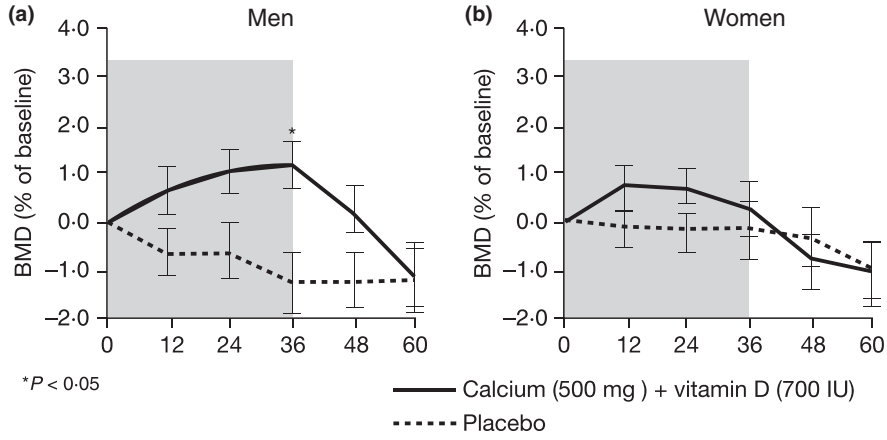

Fig. 4 Mean changes in bone mineral density (BMD) at the femoral neck in 295 women and men during (shaded area) and after calcium and vitamin D supplementation (adapted from Ref. 65). *P<0.05; The other points are not significant. Reproduced with permission by the American Journal of Clinical Nutrition. © Am J Clin Nutr. American Society for Clinical Nutrition.

remodelling that occurred with supplementation was also lost. Indeed, increased bone turnover seems to occur almost immediately after cessation of calcium and vitamin D therapy; a study by Prestwood and colleagues[66] revealed that markers of bone resorption – urinary hydroxyproline, free pyridinoline and deoxypyridinoline crosslinks, and N-telopeptides of type I collagen – returned to baseline within 6 weeks ($P < 0{\cdot}05$). PTH levels also returned to baseline levels within 6 weeks of treatment cessation.

Given the rapid reversal of the benefits of calcium and vitamin D supplementation on the suppression of PTH and bone remodelling, it is of vital importance that patients continuously meet current calcium and vitamin D intake requirements. Accordingly, patients living in the community in whom calcium and vitamin D is indicated should be informed of their fracture risk and the benefits of supplementation, with monitoring, and providing guidance over the long term to ensure they derive maximum benefits from this simple and inexpensive therapy.[20]

Conclusion

In conclusion, low calcium intake and poor vitamin D status are key determinants of osteoporosis and fracture risk. Calcium and

vitamin D supplementation is an essential component of management strategies for the prevention and treatment of osteoporosis and osteoporotic fractures. It improves bone mineralization, corrects secondary hyperparathyroidism and prevents falls. There is a general consensus that patients receiving antiresorptive (or anabolic) therapy for documented osteoporosis should receive supplementation unless calcium intake and vitamin D status are known to be optimal. Evidence suggests that the majority of these patients have a low calcium intake and/or vitamin D insufficiency. For elderly individuals, treated for primary disease prevention, supplementation with calcium and vitamin D should be targeted to those at high risk of being calcium and vitamin D insufficient, that is, those aged >70 years, housebound or institutionalized and those with low dairy intake. Routine supplementation of all elderly is not evidence-based. Serum 25(OH)D levels below 50 nmol/l indicate vitamin D insufficiency. Supplementation should therefore generally aim to increase 25(OH)D levels to the 50–75 nmol/l range. This target is achievable with a vitamin D dose of 800 IU/day, the dose that has been used in most successful fracture prevention studies. A clinical intervention trial assessing whether higher vitamin D doses achieve a greater reduction of fracture incidence would be of considerable interest. Calcium balance must also be optimized, with daily calcium intake requirements estimated at 1000 mg per day. When calcium and vitamin D is indicated, physicians should reinforce the need for adequate compliance to ensure maximum benefit in terms of fracture prevention. Once started, calcium and vitamin D supplementation should be continued for years since the effects will soon disappear after discontinuation.

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Competing interests/financial disclosure

Nothing to declare.

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