DOI:10.1111/j.1365-2125.2006.02612.x

The implications of a growing evidence base for drug use in elderly patients. Part 4. Vitamin D and bisphosphonates for fractures and osteoporosis

J. K. Dhesi,[1] T. J. Allain,[2] A. A. Mangoni[3] & S. H. D. Jackson[1]

[1]*Department of Health Care of the Elderly, Guy's, King's and St Thomas' School of Medicine, King's College London, London,* [2]*Department of Care of the Elderly, Southmead Hospital, North Bristol NHS Trust, Bristol, UK and* [3]*Department of Clinical Pharmacology and Centre for Neuroscience, Flinders University, Adelaide, Australia*

Correspondence
Professor S. H. D. Jackson,
Department of Health Care of the Elderly, Guy's, King's and St Thomas' School of Medicine, Bessemer Road, London SE5 9PJ, United Kingdom.
Tel: + 44 20 7346 3420
Fax: + 44 20 7346 3441
E-mail: stephen.jackson@kcl.ac.uk

Keywords
bisphosphonates, bone fractures, elderly patients, osteoporosis, randomized controlled trials, vitamin D

Received
21 September 2005
Accepted
2 November 2005
Published *OnlineEarly*
2 March 2006

Fractures are common in elderly subjects, disabling and occasionally fatal. Their incidence increases exponentially with age, with the commonest affected sites being the wrist, vertebrae, hip and humerus. Of these, hip fractures are the most relevant in terms of morbidity and financial cost. The increase in fracture rate with age is believed to result predominantly from age-related increases in the incidence of osteoporosis and falls. This article reviews the evidence for the use of vitamin D and bisphosphonates for the prevention of bone fractures and osteoporosis in elderly patients.

Vitamin D and fractures

Introduction

Vitamin D insufficiency plays an important role in age-related osteoporosis, as a consequence of its association with secondary hyperparathyroidism [1]. Furthermore, vitamin D insufficiency is associated with deterioration in neuromuscular function and thereby increased risk of falls [2, 3]. It has therefore been postulated that vitamin D supplementation reduces fracture rate by direct effects on bone metabolism and indirectly by reducing the incidence of injurious falls.

As vitamin D insufficiency is common in the general older population and particularly in hip fracture patients, clinical trials have focused on vitamin D supplementa-

tion in this age group [4, 5]. Therefore, the evidence base for vitamin D supplementation in the prevention of fractures in elderly patients is reliable. However, studies have used different metabolites and doses and some used additional calcium, leading to difficulty in interpretation and the establishment of clinical guidelines. Unfortunately, not all studies reported on falls incidence. In this section, clinical trials of various forms of vitamin D supplementation (with and without calcium) in the prevention of fracture in older adults are summarized (Table 1 and Figure 1).

Ergocalciferol

In a quasi randomized study, Heikinheimo et al. administered an annual intramuscular injection of ergocalciferol (150 000–300 000 IU) to two groups of subjects: community dwelling subjects aged over 85 years and institutionalized people aged 75–84 years. Follow-up was for 2–5 years [6]. A fracture rate of 16.4% was observed in the treatment group and 21.8% in the control group [6]. There was no difference between the community-dwelling and institutionalized subjects and, as expected, females had a higher rate of fracture than males (22.2% *vs.* 9.5%) [6]. Interestingly, upper limb and rib fracture rates were lower in the treated group than the control. However, there was no difference in lower limb fracture rate [6]. This study has been criticized for its design, quasi randomization, lack of blinding and placebo, and its statistical analysis. Subjects who declined the injection were added to the control group and the cumulative analysis did not include confidence limits despite the decreasing numbers with longer follow-up. Despite the criticisms, this study did identify the potential use of ergocalciferol as an important method for prevention of fractures.

A more recent study using annual intramuscular injection of ergocalciferol (300 000 IU) has provided negative results in terms of prevention of hip and other nonvertebral fractures. Furthermore, there was no observed effect when the cohort was stratified by age, mobility or previous fracture. This work has been presented in abstract form only and further details are awaited [7]. The lack of effect may relate to insufficient dosage of ergocalciferol and it will be interesting to study the baseline and post-treatment concentrations of 25-OHD. Furthermore, previous work has suggested that intramuscular ergocalciferol is inconsistent in raising serum 25-OHD concentrations due to variable absorption and that vitamin D_2 is less efficient than vitamin D_3 at increasing 25-OHD concentrations [8, 9].

Cholecalciferol (vitamin D_3)

Lips et al. conducted a prospective double-blind placebo controlled trial of oral cholecalciferol (400 IU) in community and institutionalized patients [10]. Fifty-eight hip fractures were observed in the intervention group and 48 in the placebo group ($P = 0.39$). Furthermore, there was no significant difference in other peripheral fracture rates [10]. The negative results from this study may be explained by the characteristics of the population as (a) the patients were physically fit and had good diets with high calcium content and (b) the dose of supplementation was too low. Indeed, the postintervention 25-OHD concentration in the treatment group was only 24 μg l^{-1}, which may be insufficient to prevent secondary hyperparathyroidism [10].

Trivedi et al. conducted a randomized controlled trial of oral vitamin D_3 alone (100 000 IU 4 monthly) in healthy ambulatory subjects [11]. 25-OHD concentrations increased from 21.2 μg l^{-1} to 28.4 μg l^{-1}. A 22% reduction (absolute risk reduction (ARR) 2.3%, $P = 0.04$) in total fractures and a 33% reduction (ARR 2.0%, $P = 0.02$) in fractures at major osteoporotic sites were observed [11]. These findings contrast with the study by Lips et al. and may be attributed to the higher dose (equivalent to 800 IU day^{-1}) and the longer duration of treatment.

Cholecalciferol and calcium

Two well-designed studies have examined the effects of vitamin D and calcium supplementation in elderly subjects. Chapuy et al. studied women who were living in nursing homes or residences for the elderly [12]. In a prospective double-blind placebo controlled trial, using daily oral cholecalciferol (800 IU) and calcium (1200 mg), these authors assessed fracture rate at 18 months. Forty-three per cent fewer hip fractures were observed in the treatment group. There was also a 32% reduction of all nonvertebral fractures [12]. 25-OHD concentrations, measured in a subset, were 20.4 μg l^{-1} preintervention and 40.0 μg l^{-1} postintervention in the treatment group [12]. Bone density increased by 2.7% in the treatment group, whereas it fell by 4.6% in the placebo group [12]. It has been suggested that the early reduction in fracture rate may have been related to a reduction in falls, but it is not substantiated.

In a community-based study, Dawson-Hughes et al. conducted a double-blind prospective trial of daily oral calcium (500 mg) and cholecalciferol (700 IU) supplementation in elderly men and women without documented previous osteoporotic fractures [13]. A 33% reduction in parathyroid hormone concentrations was observed in the treatment group, even though baseline

Table 1
Clinical trials of vitamin D and calcium including elderly patients

Study	Agents and daily dose	Follow-up	Elderly participants	Women	Inclusion criteria	Primary outcome measures	Result of primary outcome		
							Incidence in active group	Incidence in placebo group	ARR *P* value
Heikinheimo et al. [6]	Yearly ergocalciferol i.m. 150 000–300 000 IU *vs.* placebo	2–5 years	NA	78.8%	Elderly patients living at home or in municipal old people's homes	Fracture rates	16.4%	21.8%	5.4% $P = 0.034$
Smith et al. [7]	Yearly ergocalciferol i.m. 300 000 IU *vs.* placebo	3 years	≥75 years (100%)	53.9%	Men and women living in the community	Hip, wrist, and nonvertebral fractures	NA	NA	NA
Lips et al. [10]	Cholecalciferol 400 IU day^{-1} orally *vs.* placebo	4 years	≥70 years (100%)	74.3%	Men and women living independently or in homes for elderly persons	Incidence of hip and other bone fractures	4.5% (hip fractures) 6.0% (other fractures)	3.7% (hip fractures) 5.7% (other fractures)	–0.8% $P = 0.39$ –0.3% $P = 0.86$
Trivedi et al. [11]	4-monthly cholecalciferol 100 000 IU *vs.* placebo	5 years	65–85 years (100%)	24.2%	Men and women living in the community	Fracture incidence and total mortality	8.8%	11.1%	2.3% $P = 0.04$
Chapuy et al. [12]	Cholecalciferol 800 IU day^{-1} and calcium 1200 mg day^{-1} orally *vs.* placebo	1.5 years	69–106 years (100%)	100%	Healthy ambulatory women	Incidence of hip fractures and other nonvertebral fractures	2.4% (hip fractures) 7.5% (other fractures)	4.2% (hip fractures) 10.9% (other fractures)	1.8% $P = 0.043$ 3.4% $P = 0.015$
Dawson-Hughes et al. [13]	Cholecalciferol 700 IU day^{-1} and calcium 500 mg day^{-1}*vs.* placebo	3 years	≥65 years (100%)	54.7%	Healthy ambulatory men and women	Bone mineral density and incidence of nonvertebral fractures	5.9%	12.9%	7.0% $P = 0.02$
Tilyard et al. [14]	Calcitriol 0.50 μg day^{-1} *vs.* calcium 1 g day^{-1}	3 years	NA	100%	Women with ≥ one vertebral compression fractures	Incidence of vertebral fractures	5.6%	20.1%	14.5% $P < 0.001$

NA not available; ARR absolute risk reduction.

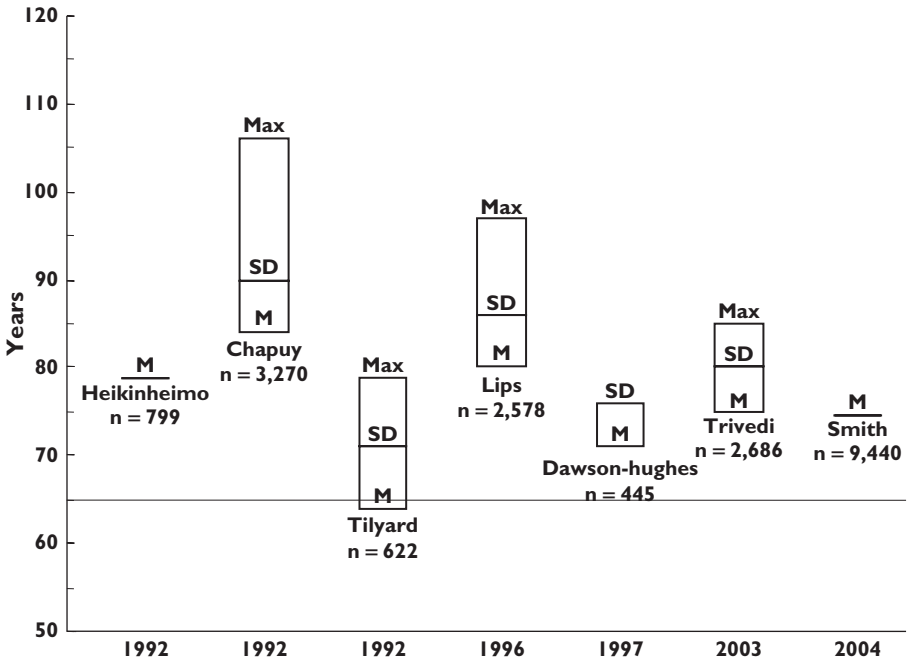

Figure 1
Age distribution of trials on vitamin D in elderly patients. M, mean age; SD, standard deviation; Max, maximum age

25-OHD was not low (28.8 μg l^{-1} in women) [13]. Furthermore, although there was no significant reduction in the incidence of falls, there was a significant reduction in total fracture rate, with 12.9% of the placebo group suffering a fracture in contrast to 5.9% of the treated group [13].

Calcitriol (1,25-dihydroxyvitamin D_3)

The only randomized controlled trial of calcitriol has been conducted in postmenopausal women with established osteoporotic vertebral fractures, randomized to calcitriol or calcium in a single-blind design [14]. New vertebral fractures were determined by radiographs. In the second and third year women receiving calcitriol had significantly fewer fractures compared with those receiving calcium [14]. There was also a reduction in peripheral fractures in those receiving calcitriol, although the study was not powered to assess this effect [14]. This study concluded that continuous treatment of postmenopausal osteoporosis with calcitriol for 3 years was safe and effective at reducing vertebral fractures. However, it is not possible to extrapolate these findings to older patients.

Safety and tolerability

In all the studies discussed vitamin D was well tolerated. However, patients with primary hyperparathyroidism, sarcoidosis, tuberculosis or lymphoma may become hypercalcaemic in response to vitamin D supplementation and should therefore be monitored closely. With the exception of these conditions, adverse effects have been noted only at concentrations >140 nmol l^{-1}, which would require a total vitamin D supply of 10 000 IU day^{-1} [15].

Discussion

Osteoporotic fractures predominantly occur in those aged over 65 years. Therefore, the role of vitamin D in the prevention of fractures has been studied specifically in this population, providing a good evidence base for elderly people. Studies on vitamin D have included patients up to the age of 105 years (Figure 1). However, confusion remains regarding the relative benefit of vitamin D alone as opposed to vitamin D and calcium. Furthermore, studies to date have not deciphered the relative contribution of a reduction in falls incidence to the overall reduction in fracture rate. Nevertheless, in the prevention of osteoporotic fractures the current evidence base favours the use of cholecalciferol (800 IU daily) above ergocalciferol, with concurrent calcium use (500–1200 mg daily), a cheap and effective regimen.

Bisphosponates and osteoporosis

Introduction

Bisphosphonate drugs are analogues of inorganic pyrophosphate that bind to bone mineral and inhibit osteoclast bone resorption, leading to a reduction in bone turnover. Bisphosphonates have been used for the treatment of postmenopausal osteoporosis since the early 1990s. They should only be used in subjects who are

known to be calcium and vitamin D replete. Several large, placebo-controlled, randomised trials have demonstrated the fracture reduction efficacy of bisphosphonates (Table 2 and Figure 2).

Etidronate

Two randomized controlled trials published in 1990 demonstrated that intermittent cyclical etidronate reduced vertebral fractures by about 50% but had no significant effect on nonvertebral fractures [16, 17]. Both studies recruited postmenopausal women ≤75 years presenting with at least one vertebral fracture. Storm et al. studied 66 women with a mean age of 68 years [16]. After the first year of treatment new vertebral fractures were significantly reduced in the etidronate group (6 *vs.* 54 per 100 patient years, $P < 0.023$) [16]. In a study of 429 women with a mean age of 65 years, Watts et al. demonstrated reduced vertebral fractures and noted that the lower the bone mineral density at outset the greater the benefit [17].

Lack of evidence for nonvertebral fracture reduction, poor oral absorption requiring a 4 h fast, and a complicated cyclical treatment regime, mean that the newer, and more potent, amino-bisphosphonates, alendronate and risedronate have largely replaced etidronate, both from the perspective of efficacy and acceptability. The randomized controlled trials examining the effectiveness of alendronate and risedronate are characterized by impressively large sample sizes and recruitment of older subjects (i.e. up to the age of 80 years in the alendronate studies and 85 years in the risedronate studies).

Alendronate

A phase 3 study of women with osteoporosis diagnosed on the basis of low bone mineral density showed a significant reduction in new vertebral fractures after 3 years treatment with alendronate [18]. In this study there was a suggestion that patients >65 years had more benefit than patients <65 years and those with vertebral fractures had more benefit than those without. Because the incidence of vertebral fractures rises with age these observations may be related [18]. The study was not powered to look at a reduction in nonvertebral fractures and showed an insignificant trend in this direction [18].

The FIT (Fracture Intervention Trial) followed women, with osteoporosis diagnosed on the basis of low bone mineral density, divided into two groups depending whether they also had vertebral fractures. Those in the fracture group were slightly older compared with the nonfracture group [19, 20]. Bone mineral density was slightly higher in the nonfracture group. After 3 years of alendronate treatment both groups showed a significant reduction in the incidence of new vertebral fractures. The reduction was greater in women with previous vertebral fractures (ARR 7.0%, $P = 0.001$ *vs.* ARR 1.7%, $P = 0.002$) [19, 20]. Hip fractures were reduced by 50% in women with prior vertebral fractures, but in the cohort of women without prior fracture only those with established osteoporosis on the basis of their bone mineral density had a significant reduction in hip fracture. Thus, the greatest benefit of treatment was in those with more severe disease [19, 20].

The ability of alendronate to prevent nonvertebral fractures in women with low bone mineral density, but without prior fracture, has been confirmed in the FOSIT (Fosamax International Trial) study [21]. The women in this study were younger than the FIT subjects, with a mean age of 62.8 years. Treatment with alendronate for 1 year significantly increased bone mineral density and reduced the incidence of nonvertebral fractures *vs.* placebo [21]. A subsequent analysis of the FIT data has examined tolerability of alendronate with increasing age. Although initial analysis showed increased side-effects in older women, study drop out rates were no higher in older, compared with younger women, once self-rated health and depressive symptoms had been controlled for [22].

Risedronate

The major randomized controlled trials examining the fracture prevention efficacy of risedronate recruited women up to age 85 years, but unfortunately, with the exception of the Hip Intervention Program (HIP) study [23], the authors do not specify what proportion of the sample were aged over 80 years and the average ages are equivalent to the alendronate data.

In the VERT-NA (Vertebral Efficacy with Risedronate Therapy-North America) and VERT-MN (Vertebral Efficacy with Risedronate Therapy-MultiNational) studies postmenopausal women with low bone mineral density and vertebral deformity received risedronate for 3 years [24, 25]. In the North American study new vertebral fractures were reduced by 41% and nonvertebral fractures by 39% [24]. The corresponding figures for the multinational study were 49% and 33% [25].

The HIP study was potentially the most informative study addressing the efficacy of bisphosphonates in very elderly patients. Unfortunately the recruitment criteria were such that no benefit of treatment was demonstrated in this group [23]. After 3 years of treatment there was a 40% reduction in hip fracture. The cohort of women aged 80–85 years were recruited on the basis of the presence of clinical risk factors for fracture or a low bone mineral density. In this group, hip fracture was

Table 2
Clinical trials on bisphosphonates including elderly patients

Study	Agents and daily dose	Follow-up	Elderly participants	Inclusion criteria	Primary outcome measures	Result of primary outcome		
						Incidence in active group	Incidence in placebo group	ARR *P* value
Storm *et al.* [16]	Etidronate 400 mg day^{-1} *vs.* placebo	2.9 years	NA	Postmenopausal women with osteoporosis	Bone mineral density and fracture rate	NA	NA	NA
Watts *et al.* [17]	Etidronate 400 mg day^{-1} *vs.* Placebo or phosphate 1.0 g day^{-1}	2 years	NA	Women with osteoporosis who had been post-menopausal for ≥ 12 months	Changes in bone mineral density and rate of new vertebral fractures	4.1%	9.3%	5.2% $P = 0.044$
Liberman *et al.* [18]	Alendronate 5–20 mg day^{-1} *vs.* placebo	3 years	≥ 65 years (39.9%)	Postmenopausal women with osteoporosis	Changes in bone mineral density and rate of new vertebral fractures	3.2%	6.2%	3.0% $P = 0.03$
FIT-I [19]	Alendronate 5–10 mg day^{-1} *vs* placebo	4.2 years	65–74 years (53.1%) 75–80 years (13.0%)	Postmenopausal women with no vertebral fractures	Changes in bone mineral density and rate of new fractures	12.3%	14.1%	1.8% $P = 0.07$
FIT-II [20]	Alendronate 5–10 mg day^{-1} *vs.* placebo	2.9 years	65–74 years (57.1%) 75–81 years (26.6%)	Postmenopausal women with vertebral fractures	Rate of new vertebral fractures	8.0%	15.0%	7.0% $P < 0.001$
FOSIT [21]	Alendronate 10 mg day^{-1} *vs.* placebo	1 year	NA	Postmenopausal women with low bone mineral density	Changes in bone mineral density and incidence of nonvertebral fractures	2.0%	3.9%	1.9% $P = 0.021$
VERT-NA [25]	Risedronate 2.5–5.0 mg day^{-1} *vs.* placebo	3 years	NA	Postmenopausal women with osteoporosis and ≥ one vertebral fracture	Changes in bone mineral (density and incidence of vertebral and nonvertebral fractures	11.3% (vertebral fractures) 5.2% (other fractures)	16.3% (vertebral fractures) 8.4% (other fractures)	5.0% $P = 0.003$ 3.2% $P = 0.02$
VERT-MN [24]	Risedronate 2.5–5.0 mg day^{-1} *vs.* placebo	3 years	NA	Postmenopausal women with osteoporosis and ≥ two vertebral fractures	Incidence of new vertebral fractures	18.1%	29.0%	10.9% $P < 0.001$
HIP [23]	Risedronate 2.5–5.0 mg day^{-1} *vs.* placebo	3 years	70–79 years (58.3%) ≥ 80 years (41.7%)	Postmenopausal women with osteoporosis or ≥ one nonskeletal risk factor for osteoporosis	Occurrence of hip fractures	2.8%	3.9%	1.1% $P = 0.02$
Ringe *et al.* [27]	Alendronate 10 mg day^{-1} *vs.* 1-alphacalcidol	3 years	NA	Men with established osteoporosis	Changes in bone mineral density and fracture rate	10.3%	24.2%	13.9% $P = 0.004$

NA, not available; ARR, absolute risk reduction.

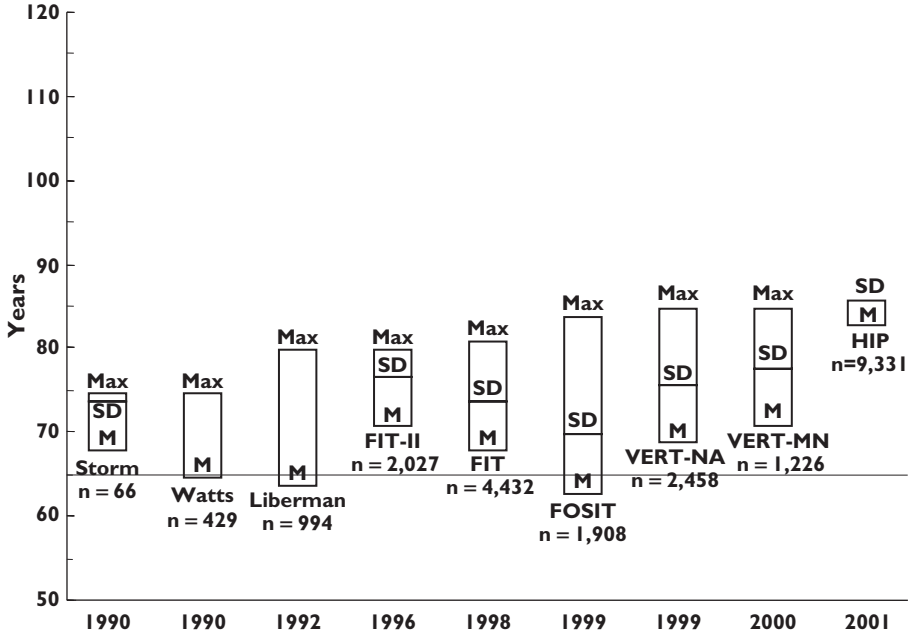

Figure 2
Age distribution of trials on bisphosphonates in elderly patients. M mean age; SD: standard deviation; Max maximum age

only reduced by 20% (ARR 0.9%, $P = 0.35$), presumably because the sample included a large number of women who were not osteoporotic [23]. Subsequent analysis, combining the very elderly patients (i.e. the 80–85 years old subjects) from all three studies (VERT-NA, VERT-MN and HIP) showed an 81% reduction in vertebral fracture (ARR 8.4%, $P < 0.01$) in the first year of treatment [26]. The combined analysis of these three studies was also useful as it demonstrated that bisphosphonate treatment was well tolerated in this age group, with a side-effect profile equivalent to placebo [26].

Osteoporosis in men

The evidence for the use of bisphosphonates to prevent and treat primary osteoporosis in men is much more limited. The majority of studies have used changes in bone mineral density as a primary endpoint, rather than fracture prevention. Improvements in bone mineral density are equivalent to those seen in women and, on this basis, bisphosphonate treatment is advocated in men. In an open label study, alendronate reduced new vertebral fractures more effectively than calcitriol in 134 men with primary osteoporosis. New vertebral fractures occurred in 24.2% of the calcitriol-treated patients and in 10.3% of the alendronate-treated patients [27]. Alendronate, but not risedronate, is licensed for the treatment of male osteoporosis in the UK.

Discussion

The studies presented overwhelmingly demonstrate the fracture prevention efficacy of bisphosphonate drugs in postmenopausal women ≤85 years with established osteoporosis, confirmed by bone mineral density measurement, with or without vertebral fractures. The data also suggest that the more severe the osteoporosis the greater the benefits of treatment. Because bone density continues to decline, even into very old age, and vertebral fracture prevalence rises rapidly after the age of 75 years it is likely that very old patients, even those over 85 years, will benefit more from treatment than younger women. The studies are also reassuring in that side-effects of treatment are no more common in very old patients.

References

1 Ringe JD. Vitamin D deficiency and osteopathies. Osteoporos Int 1998; 8(Suppl 2): S35–S39.
2 Dhesi JK, Bearne LM, Moniz C, Hurley MV, Jackson SH, Swift CG, Allain TJ. Neuromuscular and psychomotor function in elderly subjects who fall and the relationship with vitamin D status. J Bone Miner Res 2002; 17: 891–7.
3 Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res 2000; 15: 1113–8.
4 Scharla SH. Prevalence of subclinical vitamin D deficiency in different European countries. Osteoporos Int 1998; 8(Suppl 2): S7–12.
5 Baker MR, McDonnell H, Peacock M, Nordin BE. Plasma 25-hydroxy vitamin D concentrations in patients with fractures of the femoral neck. BMJ 1979; 1: 589.

6 Heikinheimo RJ, Inkovaara JA, Harju EJ, Haavisto MV, Kaarela RH, Kataja JM, Kokko AM, Kolho LA, Rajala SA. Annual injection of vitamin D and fractures of aged bones. Calcif Tissue Int 1992; 51: 105–10.

7 Smith H, Anderson F, Raphael H, Crozier S, Cooper C. Effect of annual intramuscular vitamin D supplementation on fracture risk: population-based, randomised, double-blind, placebo-controlled trial. Osteoporos Int 2004; 15: S8.

8 Whyte MP, Haddad JG Jr. Variable potency of intramuscular vitamin D preparations. N Engl J Med 1979; 300: 142.

9 Trang HM. Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R. Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. Am J Clin Nutr 1998; 68: 854–8.

10 Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med 1996; 124: 400–6.

11 Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003; 326: 469–71.

12 Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med 1992; 327: 1637–42.

13 Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997; 337: 670–6.

14 Tilyard MW, Spears GF, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. N Engl J Med 1992; 326: 357–62.

15 Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 1999; 69: 842–56.

16 Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990; 322: 1265–71.

17 Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, Jackson RD, Licata AA, Ross P, Woodson GC, III, Yanover MJ. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990; 323: 73–9.

18 Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW, Jr., Dequeker J, Favus M. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995; 333: 1437–43.

19 Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998; 280: 2077–82.

20 Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996; 348: 1535–41.

21 Pols HA, Felsenberg D, Hanley DA, Stepan J, Munoz-Torres M, Wilkin TJ, Qin-sheng G, Galich AM, Vandormael K, Yates AJ, Stych B. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Foxamax International Trial Study Group. Osteoporos Int 1999; 9: 461–8.

22 Buist DS, LaCroix AZ, Black DM, Harris F, Blank J, Ensrud K, Edgerton D, Rubin S, Fox KM. Inclusion of older women in randomized clinical trials: factors associated with taking study medication in the fracture intervention trial. J Am Geriatr Soc 2000; 48: 1126–31.

23 McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001; 344: 333–40.

24 Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I, Eastell R. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000; 11: 83–91.

25 Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut CH, III, Brown J, Eriksen EF, Hoseyni MS, Axelrod DW, Miller PD. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. JAMA 1999; 282: 1344–52.

26 Boonen S, McClung MR, Eastell R, El Hajj FG, Barton IP, Delmas P. Safety and efficacy of risedronate in reducing fracture risk in osteoporotic women aged 80 and older: implications for the use of antiresorptive agents in the old and oldest old. J Am Geriatr Soc 2004; 52: 1832–9.

27 Ringe JD, Dorst A, Faber H, Ibach K. Alendronate treatment of established primary osteoporosis in men: 3-year results of a prospective, comparative, two-arm study. Rheumatol Int 2004; 24: 110–3.