SAGE-Hindawi Access to Research
Journal of Osteoporosis
Volume 2011, Article ID 875249, 6 pages
doi:10.4061/2011/875249

Research Article

Calcium and Vitamin D Supplementation in Men

Evelien Gielen,[1,2,3] Steven Boonen,[1,2,3] Dirk Vanderschueren,[3,4] Mieke Sinnesael,[4] Annemieke Verstuyf,[4] Frank Claessens,[5] Koen Milisen,[1,6] and Sabine Verschueren[7]

[1] *Division of Geriatric Medicine, Leuven University Hospital, Herestraat 49, 3000 Leuven, Belgium*
[2] *Gerontology and Geriatrics Section, Department of Experimental Medicine, K.U.Leuven, 3000 Leuven, Belgium*
[3] *Leuven University Centre for Metabolic Bone Diseases, 3000 Leuven, Belgium*
[4] *Experimental Medicine and Endocrinology, Department of Experimental Medicine, K.U.Leuven, 3000 Leuven, Belgium*
[5] *Molecular Endocrinology Laboratory, Department of Molecular Cell Biology, K.U.Leuven, 3000 Leuven, Belgium*
[6] *Centre for Health Services and Nursing Research, K.U.Leuven, 3000 Leuven, Belgium*
[7] *Research Centre for Musculoskeletal Rehabilitation, Department of Rehabilitation Sciences, K.U.Leuven, 3000 Leuven, Belgium*

Correspondence should be addressed to Steven Boonen, steven.boonen@uzleuven.be

Received 13 April 2011; Accepted 4 July 2011

Academic Editor: Pawel Szulc

Calcium and vitamin D supplements reverse secondary hyperparathyroidism and are widely prescribed to prevent osteoporotic fractures, with proven antifracture efficacy when targeted to individuals with documented insufficiencies. Men who should particularly be considered for calcium and vitamin D supplements include elderly or institutionalized individuals, patients with documented osteoporosis on antiresorptive or anabolic medication, and individuals receiving glucocorticoids. Benefits are most apparent when a daily dose of 1000–1200 mg calcium is complemented with 800 IU vitamin D. Compliance is the key to optimizing clinical efficacy. While (conventionally dosed) vitamin D has not been associated with safety concerns, recent meta-analytic data have provided evidence to suggest that calcium supplements (without coadministered vitamin D) may potentially be associated with cardiovascular risks.

1. Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility [1]. Together with the age-related increase in the risk of falling, this compromised bone strength results in an increased fracture risk [2]. Key determinants of this age-related bone fragility are calcium intake and levels of vitamin D, which promotes intestinal calcium absorption [3]. In older individuals, low dietary calcium intake and vitamin D deficiency are common because of less sunlight exposure, reduced capacity of the skin for vitamin D synthesis, inadequate vitamin D dietary intake, or less efficient intestinal absorption of vitamin D, resulting in a negative calcium balance. This stimulates the secretion of parathyroid hormone (PTH) and induces age-associated secondary hyperparathyroidism, which enhances bone turnover and accelerates bone loss [4]. Additionally, vitamin D deficiency leads to muscle weakness and increases the risk of falling [5], low physical performance [6], and dynamic and postural instability [7].

Taken together, low serum calcium and vitamin D deficiency increase fracture risk by enhancing bone metabolism as well as by increasing the risk of falling. Substitution with calcium and vitamin D reduces both bone loss and the risk of falling and is therefore recommended as first-line strategy in the prevention and treatment of osteoporosis and osteoporotic fractures. Guidelines typically apply this recommendation to both men and women, although most individual trials and meta-analyses have only or mainly included women, with limited data in men [8]. This paper reviews the existing evidence for the effect of calcium and vitamin D supplementation on bone mineral density (BMD), muscle strength, and the risk of falls and fractures in men.

2. Effect of Calcium and Vitamin D on Secondary Hyperparathyroidism, Bone Mineral Density, and Bone Turnover

Both calcium and vitamin D supplements *reverse the age-associated secondary hyperparathyroidism* in older individuals. This reduction in serum PTH is greater with combined calcium and vitamin D supplementation than with vitamin D alone [3] and depends on baseline calcium balance, with the greatest effect of supplementation observed in individuals with the lowest calcium intake and/or vitamin D levels [9]. Gender, however, apparently is an independent determinant of serum vitamin D [10], and to keep PTH within the normal range, women seem to require higher levels of vitamin D than men [11].

A decrease in levels of PTH is associated with an *increase in BMD*, as has been demonstrated in a recent meta-analysis in more than 40000 men and women aged 50 years and older [12]. In this meta-analysis of 24 trials reporting BMD as an outcome, 19 trials included only women, while four trials included men and women [13–16], and one trial included only men [17]. Of the five trials that included men, two trials determined the difference in bone loss between calcium in monotherapy (±750 mg per day) and placebo [13, 15], while the others compared calcium (500 mg to 1000 mg per day) plus vitamin D (500 IU to 1000 IU per day) with placebo [14, 16, 17]. Overall, treatment with calcium plus vitamin D or with calcium alone was associated with a significantly reduced rate of bone loss at the hip and spine. No subgroup analyses were performed to evaluate the influence of sex on treatment effect on BMD, but in line with the overall conclusion of this meta-analysis, reduced bone loss was seen in most of the studies that included men [13–16]. However, the one available men-only trial could not demonstrate a reduction of bone loss in spite of supplementation with 1000 mg calcium and 1000 IU vitamin D per day during three years [17]. This negative result may reflect the high baseline dietary calcium intake in the men included in the study (1160 mg per day) compared to lower doses of calcium in the other trials, such as a daily dose of 700 mg calcium [14] or less (550 mg [15]), supporting the concept that substitution therapy only makes sense when calcium balance is negative.

The decrease in PTH with calcium and vitamin D supplementation is also associated with *reduced bone turnover* [15, 16]. Meier et al. observed that calcium and vitamin D supplementation during winter prevented seasonal changes in PTH and bone loss in both men and women, although the effect on bone turnover was stronger in women. In this context, it should be noted that seasonal changes of bone turnover markers are only significant in women and almost absent in men [16].

3. Effect of Calcium and Vitamin D on Muscle Strength and the Risk of Falls

Supplementation with calcium and vitamin D not only reduces bone loss but also reduces the risk of falling by improving muscle strength, muscle function, and balance [7, 18, 19]. Vitamin D receptors (VDRs) are present in skeletal muscle cells and may account for these effects [20, 21]. In a recent meta-analysis, vitamin D therapy (200–1000 IU per day) lowered the risk of falling with 14% (RR 0.86, 95% CI 0.79–0.93) compared with calcium or placebo [22]. In this meta-analysis of ten trials, the number needed to treat with vitamin D to prevent one fall was 15, and—although a dose of 800 IU vitamin D or greater was most effective—a significantly lower fall risk was also seen with 400 IU [22].

In an earlier meta-analysis of eight double blind randomized controlled trials, on the other hand, a 19% fall reduction (RR 0.81, 95% CI 0.71–0.92) was only observed with a dose of at least 700 IU vitamin D per day and a 23% fall reduction (RR 0.77, 95% CI 0.65–0.90) with serum vitamin D concentrations of at least 60 nmol/L (24 ng/mL), while less than 700 IU vitamin D per day did not reduce fall risk (RR 1.10, 95% CI 0.89–1.35) [23]. Subgroup analyses were unable to document a significant reduction in falls in men but the subset was small ($N = 211$) and the analyses underpowered. In an earlier meta-analysis of the effect of vitamin D on falls, sex-specific subgroup analyses suggested that the fall-preventing effect of vitamin D is independent of sex: vitamin D reduced the odds ratio of falling in men by 21% (OR 0.79, 95% CI 0.57–1.1; $P = 0.17$) and in women by 19% (OR 0.81, 95% CI 0.65–1.00; $P = 0.05$). Again, the result of the sex-specific subgroup analysis in men was not significant due to the small number of men in the included trials, but numerically similar to the reduction seen in women [24].

Future research should determine the optimal dose of vitamin D to prevent falls, but available evidence suggests that men benefit to a similar extent as women.

4. Antifracture Efficacy of Calcium and Vitamin D

A negative calcium balance contributes to fracture risk by enhancing bone degradation through secondary hyperparathyroidism and by increasing the risk of falling through a negative effect on muscle strength, muscle function, and balance. Substitution with calcium and vitamin D is therefore considered the first-line strategy in the prevention of osteoporotic fractures. To establish the antifracture efficacy of substitution, several individual trials and meta-analyses have been performed with calcium or vitamin D alone or combined calcium plus vitamin D.

4.1. Effect of Calcium or Vitamin D Alone on Fracture Risk. Meta-analyses comparing the effect of calcium alone with placebo showed that calcium in monotherapy does not significantly reduce fracture risk [25, 26]. Of these meta-analyses, one included only women [25], while the other included both genders and conducted sex-specific analyses on the reduction of hip fracture risk [26]. Although data in men were limited, this meta-analysis did not reveal a differential effect of calcium in men or women: in both sexes calcium in monotherapy was unable to reduce (hip) fracture risk.

The same holds true for the effect of vitamin D alone versus placebo: a meta-analysis of four randomized controlled trials ($N = 9083$) showed that vitamin D alone was insufficient for fracture prevention, even when trials with vitamin D used in higher dose (700–800 IU per day) were evaluated separately [27]. A more recent meta-analysis came to the same conclusion: irrespective of sex, 400 to 800 IU vitamin D alone is no more effective in preventing fractures than placebo [28].

These results should not come as a surprise because the negative calcium balance in older and institutionalized adults is often the result of insufficiencies in both calcium and vitamin D. For example, community-dwelling French women aged 75–90 years had a mean daily calcium intake of just 569 mg and 39% had a serum vitamin D less than 30 nmol/L (12 ng/mL) [29]. In another trial, 66% of institutionalized women had a daily calcium intake less than 800 mg and a serum vitamin D less than 30 nmol/L [30]. As a result, in these elderly and institutionalized individuals, supplementation with calcium alone or vitamin D alone would fail to restore calcium balance and prevent fractures [8].

4.2. Effect of Combined Calcium and Vitamin D Supplementation on Fracture Risk. A meta-analysis of six randomized controlled trials ($N = 45509$) comparing the effect of combined calcium and vitamin D supplementation with placebo [27] showed that this combination therapy, contrary to calcium or vitamin D alone, significantly reduced fracture risk. The risk reduction was 12% for all nonvertebral fractures, 18% for hip fractures, and 21% for hip fractures when the one trial in this meta-analysis that did not use 700 to 800 IU but 400 IU vitamin D [31] was excluded. Similarly, a recent Cochrane review found that calcium plus vitamin D prevented hip fractures in frail elderly [32] and the DIPART group concluded that the combination of calcium and vitamin D significantly reduced the risk of any fractures and hip fractures and probably reduced the risk of clinical vertebral fractures [28]. In their meta-analysis, the DIPART group adjusted analyses for several factors including sex and found that the risk reduction of combined calcium and vitamin D was independent of sex [28].

Compared with vitamin D alone, combined calcium and vitamin D supplementation reduced the risk for hip fractures by 25% in an indirect comparison of meta-analyses [27]. This might be explained by the greater effect of combined calcium and vitamin D on secondary hyperparathyroidism and bone loss [3]. In this context, it should be noted that the only trial that directly compared the effect of combined calcium and vitamin D supplementation with vitamin D [33] could not document a beneficial effect of the combination therapy, but this study—like many individual trials in this field—suffered from a lack of statistical power, a lack of targeting of the supplements to individuals with documented insufficiencies and a lack of compliance [27], which we will discuss in more detail later.

Finally, one meta-analysis including 17 trials compared the effect of calcium plus vitamin D with calcium alone on fractures [12]. Six of these trials included men and women, 11 included only women, and there were no men-only trials. Calcium or calcium plus vitamin D was associated with a 12% risk reduction in fractures of all types (RR 0.88, 95% CI 0.83–0.95). This treatment effect was similar across women and men, as suggested indirectly (since there were no men-only trials) by the comparison of the women-only to the mixed-sex trials. In this meta-analysis, subgroup analyses showed that reduction in fracture risk was greater in individuals with low dietary calcium intake (<700 mg per day) and in those with low serum vitamin D concentration (<25 nmol/L or <10 ng/mL). Treatment effect was most effective with at least 1200 mg calcium and at least 800 IU of vitamin D. In this particular analysis, the combination of calcium and vitamin D (RR 0.87, 95% CI 0.77–0.97) and calcium in monotherapy (RR 0.90, 95% CI 0.80–1.00) were equally effective ($P = 0.63$) in the prevention of osteoporotic fractures, a finding that is difficult to reconcile with evidence from other meta-analyses that calcium alone does not significantly reduce fracture risk [25, 26].

Overall, there is increasing evidence from several meta-analyses for a beneficial effect of combined calcium and vitamin D supplementation on fracture risk with no firm reasons to assume that men would respond differently from women. However, results of individual trials assessing fracture reduction with combined calcium and vitamin D supplementation have been inconsistent. Some of these individuals trials, such as the Women's Health Initiative (WHI) trial [31] and the RECORD trial [33], failed to demonstrate a significant reduction in fracture risk, whereas other trials found a beneficial effect of calcium and vitamin D supplementation on fracture risk [14, 30, 34]. These inconsistencies can be attributed to several factors, including differences in targeting of the supplementation and differences in compliance [8].

4.3. Determinants of Antifracture Efficacy of Calcium and Vitamin D Supplementation. To be effective, supplementation with calcium and vitamin D has to be targeted to men with documented or particularly at risk of calcium and/or vitamin D insufficiencies, while general supplementation in the community is not necessary. Except for extremely minor subsets, baseline vitamin D status was not assessed in participants of the WHI trial and the RECORD trial [31, 33]. In fact, most of these study participants were mobile, healthy, and community-dwelling, who are less likely to have vitamin D insufficiency and therefore less likely to benefit from substitution. This may have contributed significantly to the negative results of these studies [8]. Men who will benefit most from substitution therapy are older (>75 years of age) or institutionalized persons in whom calcium and vitamin D insufficiency is highly prevalent, as well as men with documented osteoporosis or receiving glucocorticoids. The addition of calcium and vitamin D to antiresorptive or anabolic therapy in patients with established osteoporosis is essential, given that calcium and vitamin D insufficiency is common in patients with osteoporosis and osteoporosis medication is most effective in calcium and vitamin D

replete individuals. Glucocorticoids suppress intestinal and renal calcium absorption and increase urinary calcium excretion, resulting in a negative calcium balance [35]. Therefore, patients on glucocorticoids are particularly prone to fractures and supplementation therapy should be initiated as soon as glucocorticoids are prescribed [3, 8]. Most meta-analyses recommend a combination of 1000 to 1200 mg calcium with 700 to 800 IU vitamin D per day [12, 27] or at least a dose in excess of 400 IU (482–770 IU) vitamin D [36]. The aim is to increase serum levels of vitamin D to the 50–75 nmol/L (20–30 ng/mL) range [37, 38].

In addition to adequate targeting of supplementation, compliance with calcium and vitamin D is critical as well, to optimize clinical efficacy. Within 6 weeks after calcium and vitamin D have been discontinued, bone remodeling resumes to pretreatment levels [39]. In line with these findings, any positive effects of calcium and vitamin D on bone density will not persist after discontinuation of the supplements [40]. Therefore, to prevent osteoporotic fractures, compliance and persistence with calcium and vitamin D are essential. However, even in relatively healthy trial participants in studies like the WHI and the RECORD trial, a significant proportion of individuals did not comply with supplementation: in both trials, estimated compliance was only 40–60% [31, 33]. The negative outcome of these trials can, at least partly, be explained by this lack of compliance and emphasizes the importance of adherence to treatment [8].

5. Safety Concerns about Supplementation

While (conventionally dosed) vitamin D has not been associated with safety concerns, a recent meta-analysis has provided evidence to suggest that calcium supplements (without coadministered vitamin D) may potentially be associated with cardiovascular risks. This safety concern may potentially be even more of an issue in men than in women. However, in the meta-analysis, sex-specific subgroup analysis showed this elevated cardiovascular risk to be independent of sex [41]. Although these findings constitute a safety signal that has to be taken seriously, the data have to be interpreted with some caution. When dietary intake was taken into account, there was no significant correlation between calcium intake and risk of infarction. In addition, there was no effect of calcium on strokes or death, none of the trials had adjudicated cardiovascular outcomes in a standardized manner, and the statistical outcome was only borderline significant. Finally, there are numerous large studies of calcium plus vitamin D that have shown no increased risk of cardiovascular events [31, 42] and studies of calcium alone that did not provide evidence of an increased cardiovascular risk with daily supplemental intake of 1200 mg calcium in women [43] or 1000 mg calcium in men [44]. Nevertheless, reassessment of the role of calcium supplements to prevent osteoporotic fractures is warranted. Because, in general, men are more at risk of heart disease than women, future studies with supplements should include cardiovascular endpoints and carefully assess safety in men.

6. Conclusion

Age-associated bone loss due to secondary hyperparathyroidism and an increased risk of falling are key determinants of osteoporosis and osteoporotic fractures. Substitution with calcium and vitamin D reduces bone loss by reversing secondary hyperparathyroidism and prevents falls by improving muscle strength, muscle function, and balance. As a result, calcium and vitamin D supplementation is generally recommended in the prevention of osteoporotic fractures. In men, data on the effect of calcium and vitamin D supplements on BMD and the risk of falls and fractures are limited. However, from the mechanism of bone loss and from the available evidence, there is no reason to assume that men would respond differently to calcium and vitamin D supplementation compared to women. Combined supplementation with 1000 to 1200 mg calcium and 800 IU vitamin D per day should be particularly considered in older or institutionalized men, men receiving glucocorticoids, and in male osteoporosis patients on antiresorptive or anabolic medication.

Conflict of Interests

The authors have no conflict of interests.

Acknowledgments

S. Boonen is a senior clinical investigator of the Fund for Scientific Research (FWO-Vlaanderen) and holder of the Leuven University Chair in Gerontology and Geriatrics. This work was supported by grant G.0488.08 from the Fund for Scientific Research (FWO-Vlaanderen) to S. Boonen. D. Vanderschueren is a senior clinical investigator of the Leuven University Hospital Clinical Research Fund.

References

[1] National Osteoporosis Foundation, *Clinician's Guide to Prevention and Treatment of Osteoporosis*, National Osteoporosis Foundation, Washington, DC, USA, 2008.

[2] R. P. Heaney, "Is the paradigm shifting?" *Bone*, vol. 33, no. 4, pp. 457–465, 2003.

[3] S. Boonen, H. A. Bischoff-Ferrari, C. Cooper et al., "Addressing the musculoskeletal components of fracture risk with calcium and vitamin D: a review of the evidence," *Calcified Tissue International*, vol. 78, no. 5, pp. 257–270, 2006.

[4] S. Boonen, D. Vanderschueren, P. Geusens, and R. Bouillon, "Age-associated endocrine deficiencies as potential determinants of femoral neck (type II) osteoporotic fracture occurrence in elderly men," *International Journal of Andrology*, vol. 20, no. 3, pp. 134–143, 1997.

[5] M. Visser, D. J. H. Deeg, and P. Lips, "Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (Sarcopenia): the longitudinal aging study Amsterdam," *Journal of Clinical Endocrinology and Metabolism*, vol. 88, no. 12, pp. 5766–5772, 2003.

[6] C. Annweiler, A. M. Schott, G. Berrut, B. Fantino, and O. Beauchet, "Vitamin D-related changes in physical performance: a systematic review," *Journal of Nutrition, Health and Aging*, vol. 13, no. 10, pp. 893–898, 2009.

[7] H. A. Bischoff-Ferrari, M. Conzelmann, H. B. Stähelin et al., "Is fall prevention by vitamin D mediated by a change in postural or dynamic balance?" *Osteoporosis International*, vol. 17, no. 5, pp. 656–663, 2006.

[8] S. Boonen, D. Vanderschueren, P. Haentjens, and P. Lips, "Calcium and vitamin D in the prevention and treatment of osteoporosis—a clinical update," *Journal of Internal Medicine*, vol. 259, no. 6, pp. 539–552, 2006.

[9] P. Lips, T. Duong, A. Oleksik et al., "A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: baseline data from the multiple outcomes of raloxifene evaluation clinical trial," *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 3, pp. 1212–1221, 2001.

[10] H. M. Perry, M. Horowitz, J. E. Morley et al., "Longitudinal changes in serum 25-hydroxyvitamin D in older people," *Metabolism*, vol. 48, no. 8, pp. 1028–1032, 1999.

[11] C. J. E. Lamberg-Allardt, T. A. Outila, M. U. M. Kärkkäinen, H. J. Rita, and L. M. Valsta, "Vitamin D deficiency and bone health in healthy adults in Finland: could this be a concern in other parts of Europe?" *Journal of Bone and Mineral Research*, vol. 16, no. 11, pp. 2066–2073, 2001.

[12] B. M. Tang, G. D. Eslick, C. Nowson, C. Smith, and A. Bensoussan, "Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis," *The Lancet*, vol. 370, no. 9588, pp. 657–666, 2007.

[13] T. Chevalley, R. Rizzoli, V. Nydegger et al., "Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients," *Osteoporosis International*, vol. 4, no. 5, pp. 245–252, 1994.

[14] B. Dawson-Hughes, S. S. Harris, E. A. Krall, and G. E. Dallal, "Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older," *The New England Journal of Medicine*, vol. 337, no. 10, pp. 670–676, 1997.

[15] M. Peacock, G. Liu, M. Carey et al., "Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60," *Journal of Clinical Endocrinology and Metabolism*, vol. 85, no. 9, pp. 3011–3019, 2000.

[16] C. Meier, H. W. Woitge, K. Witte, B. Lemmer, and M. J. Seibel, "Supplementation with oral vitamin D3 and calcium during winter prevents seasonal bone loss: a randomized controlled open-label prospective trial," *Journal of Bone and Mineral Research*, vol. 19, no. 8, pp. 1221–1230, 2004.

[17] E. S. Orwoll, S. K. Oviatt, M. R. McClung, L. J. Deftos, and G. Sexton, "The rate of bone mineral loss in normal men and the effects of calcium and cholecalciferol supplementation," *Annals of Internal Medicine*, vol. 112, no. 1, pp. 29–34, 1990.

[18] H. A. Bischoff-Ferrari, T. Dietrich, E. J. Orav et al., "Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged ≥60 y," *American Journal of Clinical Nutrition*, vol. 80, no. 3, pp. 752–758, 2004.

[19] R. Gupta, U. Sharma, N. Gupta et al., "Effect of cholecalciferol and calcium supplementation on muscle strength and energy metabolism in vitamin D-deficient Asian Indians: a randomized, controlled trial," *Clinical Endocrinology*, vol. 73, no. 4, pp. 445–451, 2010.

[20] C. Annweiler, M. Montero-Odasso, A. M. Schott, G. Berrut, B. Fantino, and O. Beauchet, "Fall prevention and vitamin D in the elderly: an overview of the key role of the non-bone effects," *Journal of NeuroEngineering and Rehabilitation*, vol. 7, no. 1, article 50, 2010.

[21] H. A. Bischoff, M. Borchers, F. Gudat et al., "In situ detection of 1,25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue," *Histochemical Journal*, vol. 33, no. 1, pp. 19–24, 2001.

[22] R. R. Kalyani, B. Stein, R. Valiyil, R. Manno, J. W. Maynard, and D. C. Crews, "Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis," *Journal of the American Geriatrics Society*, vol. 58, no. 7, pp. 1299–1310, 2010.

[23] H. A. Bischoff-Ferrari, B. Dawson-Hughes, H. B. Staehelin et al., "Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials," *BMJ*, vol. 339, article b3692, 2009.

[24] H. A. Bischoff-Ferrari, B. Dawson-Hughes, W. C. Willett et al., "Effect of vitamin D on falls: a meta-analysis," *Journal of the American Medical Association*, vol. 291, no. 16, pp. 1999–2006, 2004.

[25] B. Shea, G. Wells, A. Cranney et al., "VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis," *Endocrine Reviews*, vol. 23, no. 4, pp. 552–559, 2002.

[26] H. A. Bischoff-Ferrari, B. Dawson-Hughes, J. A. Baron et al., "Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials," *American Journal of Clinical Nutrition*, vol. 86, no. 6, pp. 1780–1790, 2007.

[27] S. Boonen, P. Lips, R. Bouillon, H. A. Bischoff-Ferrari, D. Vanderschueren, and P. Haentjens, "Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative metaanalysis of randomized controlled trials," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 4, pp. 1415–1423, 2007.

[28] DIPART Group, "Patient level pooled analysis of 68 500 patients from seven major vitamin d fracture trials in us and europe," *BMJ*, vol. 340, article b5463, 2010.

[29] M. C. Chapuy, A. M. Schott, P. Garnero, D. Hans, P. D. Delmas, and P. J. Meunier, "Healthy elderly French women living at home have secondary hyperparathyroidism and high bone turnover in winter," *Journal of Clinical Endocrinology and Metabolism*, vol. 81, no. 3, pp. 1129–1133, 1996.

[30] M. C. Chapuy, R. Pamphile, E. Paris et al., "Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the decalyos II study," *Osteoporosis International*, vol. 13, no. 3, pp. 257–264, 2002.

[31] R. D. Jackson, A. Z. LaCroix, M. Gass et al., "Calcium plus vitamin D supplementation and the risk of fractures," *The New England Journal of Medicine*, vol. 354, no. 7, pp. 669–683, 2006.

[32] A. Avenell, W. J. Gillespie, L. D. Gillespie, and D. O'Connell, "Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis," *Cochrane Database of Systematic Reviews*, no. 2, Article ID CD000227, 2009.

[33] A. M. Grant, "Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium or vitamin D, RECORD): a randomised placebo-controlled trial," *The Lancet*, vol. 365, no. 9471, pp. 1621–1628, 2005.

[34] M. C. Chapuy, M. E. Arlot, P. D. Delmas, and P. J. Meunier, "Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women," *British Medical Journal*, vol. 308, no. 6936, pp. 1081–1082, 1994.

[35] J. Iwamoto, T. Takeda, and Y. Sato, "Prevention and treatment of corticosteroid-induced osteoporosis," *Yonsei Medical Journal*, vol. 46, no. 4, pp. 456–463, 2005.

[36] H. A. Bischoff-Ferrari, W. C. Willett, J. B. Wong et al., "Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials," *Archives of Internal Medicine*, vol. 169, no. 6, pp. 551–561, 2009.

[37] B. Dawson-Hughes, A. Mithal, J. P. Bonjour et al., "IOF position statement: vitamin D recommendations for older adults," *Osteoporosis International*, vol. 21, no. 7, pp. 1151–1154, 2010.

[38] P. Lips, R. Bouillon, N. M. van Schoor et al., "Reducing fracture risk with calcium and vitamin D," *Clinical Endocrinology*, vol. 73, no. 3, pp. 277–285, 2010.

[39] K. M. Prestwood, A. M. Pannullo, A. M. Kenny, C. C. Pilbeam, and L. G. Raisz, "The effect of a short course of calcium and vitamin D on bone turnover in older women," *Osteoporosis International*, vol. 6, no. 4, pp. 314–319, 1996.

[40] B. Dawson-Hughes, S. S. Harris, E. A. Krall, and G. E. Dallal, "Effect of withdrawal of calcium and vitamin D supplements on bone mass in elderly men and women," *American Journal of Clinical Nutrition*, vol. 72, no. 3, pp. 745–750, 2000.

[41] M. J. Bolland, A. Avenell, J. A. Baron et al., "Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis," *BMJ*, vol. 341, article c3691, 2010.

[42] M. C. Chapuy, M. E. Arlot, F. Duboeuf et al., "Vitamin D3 and calcium to prevent hip fractures in elderly women," *The New England Journal of Medicine*, vol. 327, no. 23, pp. 1637–1642, 1992.

[43] J. R. Lewis, J. Calver, K. Zhu, L. Flicker, and R. L. Prince, "Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up," *Journal of Bone and Mineral Research*, vol. 26, no. 1, pp. 35–41, 2011.

[44] W. K. Al-Delaimy, E. Rimm, W. C. Willett, M. J. Stampfer, and F. B. Hu, "A prospective study of calcium intake from diet and supplements and risk of ischemic heart disease among men," *The American Journal of Clinical Nutrition*, vol. 77, no. 4, pp. 814–818, 2003.