

# Calcium and vitamin D for osteoporotic fracture prevention

## Wapń i witamina D w prewencji złamań osteoporotycznych

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It is well established that calcium and vitamin D are intimately involved in bone metabolism [1]. The facts that bone mass and therefore total body calcium decrease with age, and that vitamin D deficiency is highly prevalent [1], make it biologically plausible that supplementation would mitigate bone loss and fracture risk. The corollary however, is that calcium and vitamin D are only substrates in a milieu of equally important biochemical and physiological factors, many of which are altered in osteoporosis. Additionally, many osteoporotic patients are not calcium or vitamin D deficient. Numerous studies have examined the efficacy of supplementation. Data thus far has been inconsistent and at best show only modest reductions in bone loss and fracture risk.

A 2002 meta-analysis (25 trials) of vitamin D versus placebo found a significant 37% reduction in vertebral fractures (relative risk [RR] 0.63; 95% CI: 0.45–0.88;  $p < 0.01$ ), with a non-significant trend toward reduction in non-vertebral fractures [2]. In stark contrast, another meta-analysis in 2005 found no statistically significant effect on hip, vertebral or any new fractures with vitamin D [3]. On the other hand, Trivedi et al. [4] found that vitamin D supplementation, at a dose of 100,000 IU every 4 months, reduced the risk of any first fracture by 22% compared to placebo (RR 0.78; 95% CI: 0.61–0.99;  $p = 0.04$ ). Other studies suggest that optimal prevention of non-vertebral and hip fractures occur only in those with low baseline vitamin D levels ( $< 17$  ng/ml [ $42$  nmol/l]), who are using 700–800 IU vitamin D daily, and whose vitamin D level rose to approximately 40 ng/ml (99 nmol/l) [5].

The RECORD trial ( $n = 5292$ ) found no difference in fracture incidence after 2 years between placebo and those assigned vitamin D<sub>3</sub> 800 IU daily, or calcium 1000 mg daily,

or combination therapy [6]. However, the trial was plagued with non-compliance with only 54.5% of patients taking study treatment at the end of the study. Additionally, intention-to-treat analysis would have diluted any treatment effect. Another negative study, the Women's Health Initiative calcium and vitamin D trial, showed no significant effect on any fracture end points, but this may have been confounded by estrogen use and the relatively healthy group at low risk for fracture [7]. Instead, there was an increased risk of renal calculi by 17%.

With respect to calcium alone supplementation, a meta-analysis by Shea et al. [8] found only a small positive effect on bone mineral density. There was a non-significant trend to reduction in vertebral fractures (RR 0.77; 95% CI: 0.54–1.09). A benefit for non-vertebral fractures was not discernible (RR 0.86; 95% CI: 0.43–1.72).

The most recent attempt at answering whether calcium reduces osteoporotic bone loss and fracture risk was a meta-analysis by Tang et al. [9]. It included 29 studies ( $n = 63,897$ ) of calcium alone or calcium with vitamin D, but excluded vitamin D alone studies. Calcium alone (9 trials,  $n = 6517$ ) provided a 10% reduction in fracture risk (RR 0.9), but the 95% CI did not rule out a null effect (0.80–1.00). Calcium with vitamin D (8 trials,  $n = 46,108$ ) produced only a mild non-significant difference (RR 0.87; 95% CI: 0.77–0.97). Subgroup analysis showed statistically significant greater treatment effect for calcium dose  $> 1200$  mg daily, vitamin D dose greater than 800 IU daily, and supplementation in those with low dietary calcium intake (less than 700 mg daily). There was a non-significant trend for greater benefit in patients with low baseline vitamin D level ( $< 25$  nmol/l). With respect to age, fracture risk reduction with calcium alone or combined with vitamin D was statistically significant only for patients older than 69 years (70–79 years: RR 0.89;  $> 79$  years: RR 0.76).

The authors' assertion that the "addition of vitamin D was not shown to offer additional risk reduction over and above the use of calcium alone", should be interpreted with caution. Comparison across studies is usually limited because of inherent differences in study design and baseline characteristics, and is further compounded in this setting by significant heterogeneity. Additionally, studies of vitamin D alone were excluded, including those showing significant reduction in fracture risk.

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Received: October 25, 2007. Accepted in final form: November 7, 2007.

Declared conflict of interest. Author, Jonathan D. Adachi is consultant of Amgen, Astra Zeneca, Eli Lilly, GSK, Merck, Novartis, Pfizer, Procter & Gamble, Roche, Sanofi Aventis, Servier and takes part in clinical trials of Amgen, Eli Lilly, GSK, Merck, Novartis, Pfizer, Procter & Gamble, Roche.

Pol Arch Med Wewn. 2007; 117 (10): 441-442

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Further, recent studies have also shown that vitamin D has non-osseous benefits [1] such as prevention of falls [10], and a reduction in overall mortality [11].

The conclusion that “calcium supplementation, alone or in combination with vitamin D, is effective in the preventive treatment of osteoporotic fracture” is optimistic. A more realistic conclusion is that calcium and vitamin D supplementation provide a small to modest protection against osteoporotic fracture, especially in those older than 69 years, those with low calcium intake and vitamin D level, and in the institutionalized. We believe that, in the absence of contraindications, 1000 mg of calcium (combined dietary and supplementation) and 1000 IU of vitamin D daily should be recommended for postmenopausal women and men above 65 years.

One message should be clear though: calcium and vitamin D supplementation by itself is not sufficient to ensure optimal protection against osteoporotic bone loss and fracture in those with established osteoporosis and fractures. Despite supplementation, patients may still be at high risk of fracture. One should attempt to determine absolute fracture risk by examining age, gender, bone mineral density, and other modulating risk factors such as glucocorticoid use and prior history of a fragility fracture [12]. Those with high fracture risk should be treated with calcium and vitamin D but require additional therapy with a bisphosphonate, selective estrogen receptor modulator, parathyroid hormone, strontium or hormone replacement therapy for more effective fracture prevention.

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### From the Editor

**Synopsis:** Tang B, Eslick G, Nowson C, et al. 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. *Lancet.* 2007; 370: 657-666.

In this systematic review with metaanalysis of 29 randomised controlled trials the authors assessed the efficacy of calcium or calcium in combination with vitamin D supplementation in comparison with placebo in fractures prevention and bone loss in people aged 50 years and older. 63,897 patients were included in the analysis (92% females). Calcium (200–1600 g a day) or calcium in combination with vitamin D (200–800 IU a day) supplementation is associated with lower risk of any fracture (hip, vertebra or wrist fractures; RRR: 12%) and bone mineral density loss at the hip or in spine. The addition of vitamin D to calcium did not change treatment effect significantly.

*Prepared by: Małgorzata Bała, MD, PhD*