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ORIGINAL ARTICLE

Relationship between bone mineral density changes and risk of fractures among patients receiving calcium with or without vitamin D supplementation: a meta-regression

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Abstract
Summary Surrogate measures of fracture risk, such as effects on bone mineral density, may be of great interest to assess the efficacy of available osteoporosis treatments. Our results suggest that bone mineral density (BMD) changes cannot be used as a surrogate of anti-fracture efficacy, among patients receiving calcium, with or without vitamin D.
Introduction The purpose of this study is to examine the association between changes in bone mineral density with reduction in the risk of fractures in patients receiving calcium with or without vitamin D.
Methods We selected all randomized placebo-controlled clinical trials of calcium with or without vitamin D supplementation. To be included in this analysis, the studies were required to report both BMD (hip/proximal femur and/or lumbar spine) and the incidence of fractures. Meta-regression analyses were used to examine the associations of changes in BMD with reduction in risk of fracture over the duration of each study. The change in BMD was the difference between changes (from baseline) observed in the active treatment group and placebo group.
Results A total of 15 randomized trials (n=47,365) were identified, most of whom (77%) came from the Women's Health Initiative trial. Results show that larger increases in BMD at the lumbar spine were not associated with greater reduction in fracture risk. Concerning hip BMD changes, we found a statistically significant relationship between hip BMD changes and reduction in risk. However, results were not quite significant after excluding the both largest studies, in which BMD changes were measured in very small subset of patients. These points may have largely biased our results.
Conclusions In conclusion, there was no evidence of a relationship between BMD changes and reduction in risk of fractures among patients receiving calcium with or without vitamin D supplementation. Calcium and/or Vitamin D may reduce fracture rates through a mechanism independent of bone density.

Keywords Bone mineral density · Calcium · Fracture · Meta-regression · Vitamin D

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Introduction

Osteoporosis is a disease characterized by a decrease in bone mass and deterioration in skeletal microarchitecture, leading to increased fragility and susceptibility to fracture. Given the social and economic burden of osteoporotic fractures, the prevention of fractures is essential and has become a major public health priority. Moreover, the primary goal of treatment is to reduce the risk of fracture [1]. However, trials with fractures as the primary endpoint require a study design that is either very large or very long in order to demonstrate the anti-fracture efficacy. As a consequence, surrogate measures of fracture risk that may be more quickly and easily measured, such as effects on bone mineral density or biochemical markers of bone turnover, may be of great interest to assess the efficacy of available osteoporosis treatments.

A surrogate endpoint of a clinical trial, as defined by Temple [2], is "a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives.

Changes induced by therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint". To be a validated surrogate endpoint, three requirements must be met [3, 4]. Firstly, a valid surrogate must be correlated with the clinical endpoint. Secondly, the effect of the treatment on the surrogate endpoint must predict the effect on the clinical outcome. Lastly, the surrogate endpoint must explain a substantial proportion of the treatment effect on the clinical endpoint.

Today, calcium and vitamin D are widely recognized as essential components in osteoporosis management [1, 5, 6]. Calcium and vitamin D deficiency are important factors for bone health, because reduced calcium absorption increases parathyroid hormone concentration and accelerates the rate of bone loss, which raises the number and activity of osteoclasts that release calcium from bone. Studies analyzing the effects of calcium, alone or in combination with vitamin D, on bone loss and fractures produced conflicting results, partly because of their low statistical power to assess fracture incidence (i.e., few subjects included, short period of follow-up). Moreover, some studies only report bone mineral density (BMD) data and do not assess the impact of these agents on the risk of fractures. The validation of a surrogate marker (e.g., BMD) for fracture would allow to assess the clinical interest of calcium, alone or in combination with vitamin D, in published manuscripts with BMD data only or in new clinical studies including fewer patients and with a reduced period of follow-up. Moreover, such surrogate measures may be useful to the clinician to monitor therapy with calcium and vitamin D.

The purpose of this study was to examine the associations between changes in BMD with reductions in the risk of fractures by conducting a meta-regression of randomized placebo-controlled clinical trials of calcium, alone or in combination with oral vitamin D, in patients aged 50 years and older. The objective was to test the validation of BMD change as a surrogate of fracture incidence, for calcium with or without vitamin D treatment.

Material and methods

Search strategy and data extraction

We expanded the literature search performed by Tang et al. [7] by conducting a systematic search of English articles using MEDLINE (Ovid) and Cochrane Central Register of Controlled Trials, for the period from January 2007 to June 2010. The search terms were "bone density", "bone loss", "calcium", "fracture", and "bone fracture". The computerized searches were supplemented by a manual search of relevant references of retrieved articles and of abstracts from major meetings of bone research societies.

Eligibility and exclusion criteria were specified in advance. Data were independently extracted by two authors (VR and OB) according to data extraction forms and checked for accuracy. Jadad score was used for methodological quality assessment [8].

Eligible study

We selected all randomized controlled trials of calcium with or without vitamin D supplementation versus placebo/no treatment. To be included in this analysis, the studies were required to report both BMD changes during the follow-up and the incidence of either vertebral fractures, or nonvertebral fractures, or both. When studies reported only BMD or fracture data, the corresponding authors were contacted in order to recover missing data.

Statistical analysis

Potential publication bias was explored by drawing a funnel plot. Publication bias was formally analyzed using the Begg and Mazumdar [9] and Eger et al. tests [10].

The results were examined for heterogeneity by using formal statistical tests for heterogeneity and trial inconsistency. Between-study heterogeneity was assessed using the χ^2 distributed Cochran's Q test ($p \leq 0.10$ indicating significance). Because the power of the χ^2 test to detect heterogeneity is low when there are few trials, we quantified heterogeneity by calculating the I^2 statistic: values less than 25%, 25–50%, and more than 50% indicate low, moderate, and high heterogeneity, respectively [11].

Meta-regression analysis was used to pool the data across all trials and to examine the associations of treatment and changes in BMD with reduction in the risk of fractures over the duration of each study. To measure improvement in BMD, we subtracted the percentage change in the placebo group (baseline to end of study) from the corresponding change in the active group to calculate the percentage difference.

We plotted the improvement in BMD (vs placebo) against the log of risk ratio of fracture in each trial. Each trial was plotted as a circle whose area was proportional to the study's weight in the analysis. We assumed the presence of heterogeneity a priori, and we used random effects models to derive regression equations for the association between improvement in BMD and risk of fracture. A separate model was used for each measure of BMD changes at the end of each study: one for change in spine BMD and one for change in hip BMD.

To evaluate the impact of individual studies on the overall results, we performed a one-way sensitivity analysis by omitting one study at a time, and repeating the analysis.

Results were regarded as statistically significant if $p<0.05$. All analyses were done with Comprehensive Meta-Analysis software.

Results

A total of 15 randomized controlled trials were identified that satisfied the inclusion criteria [12–26] (Fig. 1). Egger's regression analysis showed that publication bias was present ($p=0.002$; Fig. 2). The Q statistic for heterogeneity was not significant ($p=0.13$), with the I^2 value of 30%.

In total, 47,365 individuals were analyzed, most of whom (77%) came from the Women's Health Initiative [24]. The study of Reid et al. had three-group trial, with one placebo and two experimental groups (two dosages of calcium, 600 mg/day and 1,200 mg/day) [19]. These two treated groups were analyzed separately and therefore treated as two studies. As a result, the placebo group was counted twice.

In seven trials, patients received calcium and vitamin D supplementation ($n=43,474$) [20–26], whereas in the other eight trials, they received calcium-only supplementation ($n=3,891$) [12–19] (Table 1). Data about hip BMD changes at the end of the study were available in 14 studies [12–15, 17–26] (Table 2). For the assessment of the spine BMD changes at the study endpoint, data were available in 12 studies [12–17, 19, 21, 23, 24, 26] (Table 2).

Results showed that larger increases in hip BMD from baseline to study endpoint were associated with greater reduction in fracture risk ($p=0.003$; Fig. 3). The results were basically unchanged when individual trials were removed singly (yielding 15 sensitivity models, one model for each trial that was dropped). However, these results must be interpreted with caution. In fact, the associations for change in hip BMD and risk of fractures were not quite

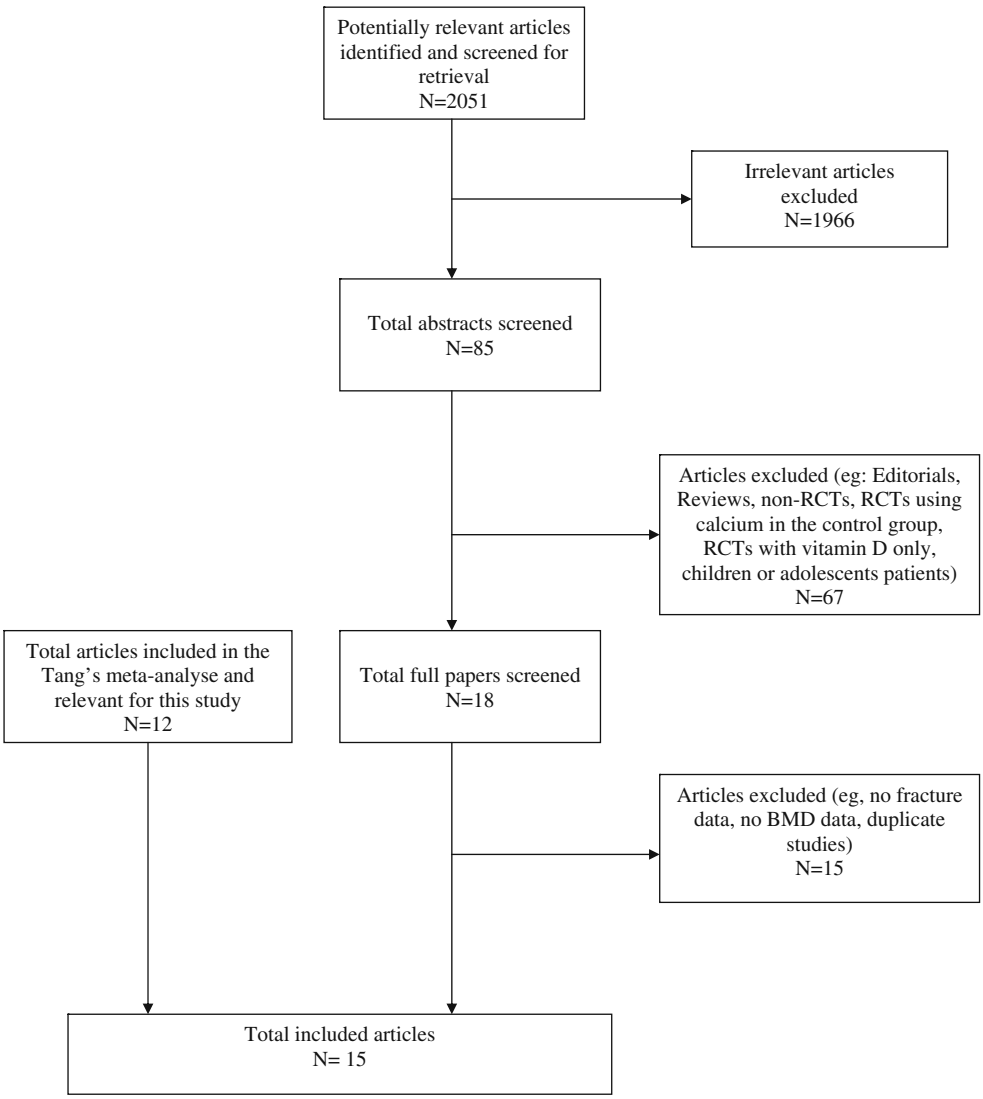

Fig. 1 Flowchart of study selection

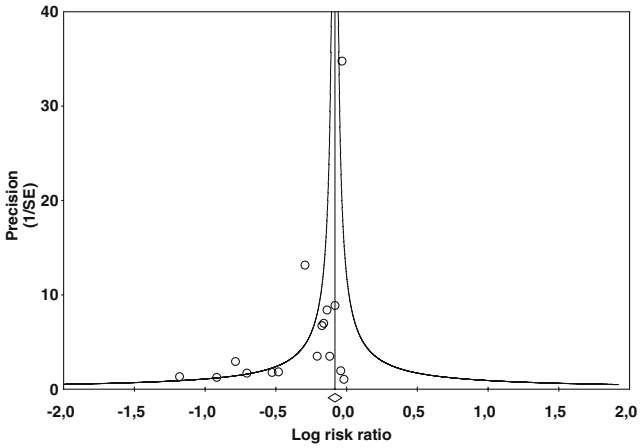

Fig. 2 Funnel plot to assess publication bias. *Circles* indicate individual studies. *Diamond* indicates summary estimates

significant after excluding the large Women's Health Initiative trial [24] and the study of Chapuy et al. [20]. Two reasons may explain these results. Firstly, the analysis is largely dominated by the Women's Health Initiative cohort because of its size. Chapuy's trial is the second largest trial included in these analyses. Moreover, it is important to note that in these both studies, BMD changes were measured in only a very small subset of the population. In the Women's Health Initiative trial and in the Chapuy's trial, BMD changes were measured respectively in only 56 women (29 women in the placebo group and 27 women in the treated group) and in 821 patients (415 women in the placebo group and 406 women in the treated group), which represents a very small subsample of the population included in these both large trials. Moreover, in the Chapuy's trial, selection of participants for which a BMD assessment was performed was not random, and therefore the results may not be generalized to the whole population included in this trial. In consequence, these points may have biased our results.

When considering changes from baseline to the study endpoint in BMD at the lumbar spine, improvements in BMD were not significantly associated with fracture risk reductions (p=0.12; Fig. 4). Results were robust in the sensitivity analysis; dropping individual trials individually from the model had no effect on the associations.

Discussion

In this study, we investigated whether BMD change from baseline can be validated as a surrogate endpoint for fracture among patients receiving calcium, alone or in combination with vitamin D. Results of this meta-regression show no significant relationship between the reduction in risk of fractures and the magnitude of the increase in BMD at the lumbar spine at the study endpoint. Concerning hip BMD changes, we found a statistically significant relationship between hip BMD changes and

Table 1 Descriptive characteristics of trials included in the meta-regression

References	Age (year), mean (SD)	Treatment	Dose (Ca/VitD)	Trial duration (months)	Number of subjects (% women)	Participants
Reid et al. [1] (1993) [12]	58 (5)	Ca	1,000 mg	24	122 (100%)	Healthy postmenopausal women
Chevalley et al. (1994) [13]	72 (7)	Ca	800 mg	18	156 (88%)	Healthy, elderly women and men
Riggs et al. (1998) [14]	66 (3)	Ca	1,600 mg	48	236 (100%)	Healthy postmenopausal women
Peacock et al. (2000) [15]	75 (8)	Ca	750 mg	48	261 (72%)	Independent, elderly women and men
Fujita et al. (2004) [16]	81	Ca	900 mg	24	19 (100%)	Institutionalized, elderly women
Reid et al. [2] (2006) [17]	74 (4)	Ca	1,000 mg	60	1,471 (100%)	Healthy postmenopausal women
Prince et al. (2006) [18]	75 (3)	Ca	1,200 mg	60	1,460 (100%)	Healthy, elderly women
Reid et al. [3] (2008)[a] [19]	57	Ca	1,200 mg or 600 mg	24	323 (0%)	Healthy men
Chapuy et al. [1] (1992) [20]	84 (6)	Ca+Vit D	1,200 mg/800 IU	18	2,790 (100%)	Women living in nursing homes or apartment houses for the elderly
Dawson-Hughes et al. (1997) [21]	71	Ca+VitD	500 mg/700 IU	36	389 (55%)	Healthy, ambulatory men and women
Chapuy et al. [2] (2002) [22]	85	Ca+VitD	1,200 mg/800 IU	24	583 (100%)	Ambulatory, institutionalized elderly women
Harwood et al. (2004) [23]	81 (range 67–92)	Ca+VitD	1,000 mg/800 IU	12	150 (100%)	Elderly women with previous fracture
Jackson et al. (WHI trial) (2006) [24]	62 (7)	Ca+vitD	1,000 mg/400 IU	108	36,282 (100%)	Healthy postmenopausal women
Bolton-Smith et al. (2007) [25]	68.6	Ca+VitD	1,000 mg/400 IU	24	244 (100%)	Healthy women
Salovaara et al. (2010) [26]	67 (2)	Ca+VitD	1,000 mg/800 IU	36	3,432 (100%)	Healthy, ambulatory postmenopausal women

[a] The study of Reid et al. [19] had three-group trial, with one placebo and two experimental groups (two dosages of calcium, 600 mg/day and 1,200 mg/day)

Table 2 Bone mineral density changes and fractures data for the trials included in the meta-regression

References	Final hip BMD[a] (%)	Final spine BMD[a] (%)	Fracture cases (*n*)	RR
Reid et al. [1] (1993) [12]	0.9[b,c]	1.6[b]	7	0.4
Chevalley et al. (1994) [13]	1.6[c]	0.55	18	0.96
Riggs et al. (1998) [14]	1.3	0.3	40	0.89
Peacock et al. (2000) [15]	2.5	2.7	41	0.81
Fujita et al. (2004) [16]	–	5.25[b]	5	0.31
Reid et al. [2] (2006) [17]	1.6	1.8	251	0.92
Prince et al. (2006) [18]	0.7 [b,c,d]	–	236	0.87
Reid et al. [3] (2008) [f] [19]	1.29[b]	0.64[b]	12	0.50
	0.23[b]	−0.36[b]	13	0.62
Chapuy et al. [1] (1992) [20]	7.3[e]	–	565	0.75*
Dawson-Hughes et al. (1997) [21]	1.2[c]	0.9	37	0.46*
Chapuy et al. [2] (2002) [22]	3.3[c, e]	–	152	0.85
Harwood et al. (2004) [23]	4.37	−0.5	11	0.49
Jackson et al. (WHI trial) (2006) [24]	1.1[e]	−0.3[b,d,e]	4260	0.97
Bolton-Smith et al. (2007) [25]	0.13[c]	–	4	0.98
Salovaara et al. (2010) [26]	−0.01[e]	0.01[e]	172	0.84

[a] Difference between changes in BMD (from baseline) observed in the active treatment group and placebo group

[b] Percentage change in BMD within each group and differences between groups were estimated from a graph in the original publication

[c] Femoral neck BMD; all other values in this table represent hip/proximal femur BMD

[d] Difference between changes in BMD (from year 1) observed in the active treatment group and placebo group

[e] BMD was measured in a subsample of the study population

[f] The study of Reid et al. [19] had three-group trial, with one placebo and two experimental groups (two dosages of calcium, 600 mg/day and 1,200 mg/day). We presented BMD changes and fractures outcomes on the first line for the Ca 1,200 mg/day group and on the second line for the Ca 600 mg/day group

*$p<0.05$

reduction in risk. However, as already mentioned, caution should be used in interpreting the results of this analysis. In fact, results were not quite significant after excluding the both largest studies included in this analysis [20, 24]. Moreover, in these both studies [20, 24], BMD changes were only measured in very small subset of patients. This may also have largely biased our results and in consequence, our results not provide a strong evidence of a relationship between BMD changes and fracture risk reduction.

Estimation of fracture risk reduction based solely on BMD changes is not supported by the current body of data. In fact, over the last decade, in the treatment of osteoporosis there has been increasing interest in quantifying the relationship between fracture endpoints and surrogates such as bone mineral density. However, studies exploring the association between BMD changes and fracture reduction have yielded contradictory results. Sarkar et al. estimated that only 4–5% of the fracture reduction observed with raloxifene treatment could be attributed to an increase in BMD [27]. Combining data from three pivotal risedronate fracture endpoint trials, Watts et al. showed that the increases in lumbar spine and femoral neck BMD account for only 18% and 11%, respectively, of the effect of risedronate on vertebral fracture incidence [28]. However, patients whose BMD decreased were at significantly greater risk of sustaining a fracture than patients whose BMD increased. Another study found that lumbar spine BMD changes accounted for about 28% of the overall risedronate treatment effect [29]. Among women treated with alendronate, Hochberg et al. found that larger increases in hip and spine BMD were associated with lower risk of vertebral fractures [30]. Women with BMD increases of at least 3% during the first 12–24 months had approximately half the incidence of new vertebral fractures compared with the small proportion of women whose BMD did not measurably increase during the first year or two of treatment. Among women treated with strontium ranelate for 3 years, Bruyère et al. found that for each percentage point increase in femoral neck or total proximal femur BMD, the risk of sustaining a new vertebral fracture decreased by 3% and 2%, respectively [31]. The changes in total proximal femur and femoral neck BMD explained 74% and 76%, respectively, of the vertebral antifracture efficacy of strontium ranelate.

Moreover, meta-analysis, using a variety of statistical methods, performed by several groups in an attempt to

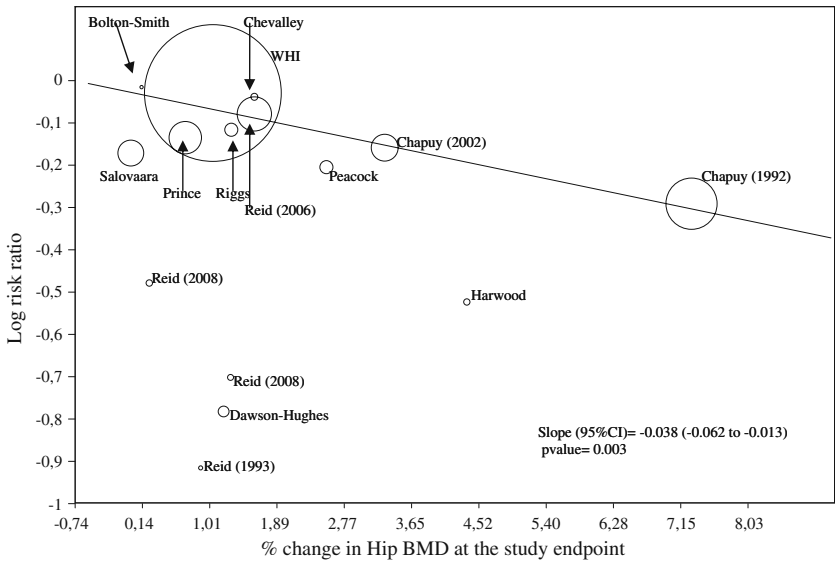

Fig. 3 Relationship between risk of fracture and change (vs Placebo) in hip BMD at the final study endpoint

resolve this issue, have produced conflicting results. Wasnich and colleagues analyzed the relationship between the increase in BMD and the reduction in vertebral fracture risk from 13 placebo-controlled trials of alendronate, etidronate, tiludronate, calcitonin, and raloxifene using Poisson regression [32]. They concluded that BMD increases explain up to half of the observed vertebral fracture risk reductions. In contrast, Cummings et al., using data from the Fracture Intervention Trial, showed that improvement in spine bone mineral density explained only 16% of the reduction in risk of vertebral fractures [33]. Moreover, using meta-analysis techniques, they demonstrated that the reductions in risk were greater than predicted from improvement in BMD. Their model estimated that antiresorptive treatments predicted to reduce fracture risk by 20%, based on improvement in BMD, actually reduce the risk of fracture by about 45%.

Hochberg et al. found a relationship between changes in BMD during the first year of antiresorptive treatment and reduction in the incidence of nonvertebral fractures occurring over the duration of studies using meta-analyses based on summary data at the trial level [34]. However, Delmas and Seeman, analyzing individual instead of group data, concluded that only a small proportion of the risk reduction in vertebral and nonvertebral fractures observed with antiresorptive treatment was explained by the increase in BMD [35]. Lastly, using individual patient data, Bauer et al. did not find a significant relationship between changes in hip or spine BMD during the first year of treatment with alendronate and subsequent reduction in nonvertebral fractures [36].

Thus, our results, as well as the results of other studies, suggest that BMD changes cannot be used as a surrogate of anti-fracture efficacy. Moreover, the poor ability of BMD

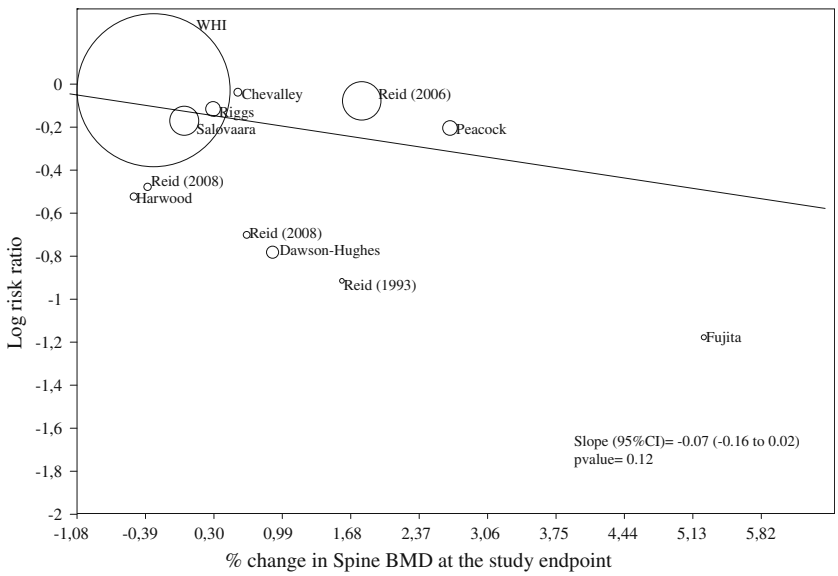

Fig. 4 Relationship between risk of fracture and change (vs Placebo) in spine BMD at the final study endpoint

changes to predict reduction of facture risk may limit its use in monitoring osteoporosis treatment, as it has been suggested by some authors [37]. In clinical practice, monitoring is particularly important during the first few years of treatment to establish therapeutic efficacy. Because not all patients who are prescribed medications for osteoporosis will maintain or have significant increases in BMD, monitoring with BMD testing can be used to identify patients who have significant decreases in BMD on therapy, decreases that can be the result of nonresponse to the treatment, poor compliance or persistence, incorrect dosing, malabsorption, or secondary causes of osteoporosis that were either unrecognized before starting treatment or developed after treatment was initiated. Therefore, in absence of other validated surrogate marker and as recommended by some guidelines [38, 39], a DXA spine and/or proximal femur study remains for most patients, the most appropriate tool for monitoring therapeutic effectiveness and identifying patients who are not adherent with treatment or who do not respond to therapy. Alternative approaches to monitoring using other surrogate markers of bone strength and fracture risk should be explored.

Our findings, as well as those from other studies assessing the relationship between changes in BMD and fracture risk reduction, raise important questions about the mechanisms underlying the improvement in bone strength associated with treatment. During treatment, the bone quality may be increased, by changing the microstructure of bone in the absence of a change in BMD. Calcium and/or Vitamin D may have anti-fracture efficacy through a mechanism independent of bone density. In addition, increases in BMD could be accompanied by formation of bone of poor quality. The relationship between BMD and fractures and the ability of BMD to predict fracture risk is also complicated by a variety of nonskeletal factors for fractures. Among them, balance and propensity to falls are significant factors. Eventually, techniques for assessing changes in bone mass may lack the precision required to quantify this relationship accurately.

Our study has some potential limitations. There is a possibility that publication bias may have influenced the results. Trials that observed positive or significant results may tend to be published more often than those that did not. Small trials that had little or no effect on BMD, but which found an apparent reduction in fracture risk simply by chance may have been published more often than similar trials that failed to find a significant effect on fractures. Another limitation is that some trials reported only fracture or BMD data, and were excluded from the analysis. In order to resolve this issue, we attempted to contact the authors but, this approach was not successful. Moreover, differences in clinical trials, such as patient's characteristics, may have influenced our findings.

We choose to perform analyses employing meta-regression based on summary statistics to quantify the underlying relationship between BMD and fracture risk reduction. As already mentioned, researchers have used a variety of statistical methods to evaluate the relationship between changes in BMD and fracture risk reduction and found varying levels of correlation between these two measurements. The proportion of fracture risk reduction explained by BMD according to these analyses varied widely. Analyses based on individual patient data have suggested that increases in BMD account for only 4–28% of reductions in fracture risk. Analyses using meta-regression based on summary statistics, however, indicated that most of the anti-fracture benefits were due to improvements in BMD.

The techniques of meta-regression based on summary statistics have several limitations [40]. Statistical power to detect useful associations using meta-regression is limited by the number of available studies [41]. Associations between aggregated values may not be representative of the true relationships in the data at the individual level. The results of meta-regression analyses may not be as robust as those of regression analyses using individual patient data. Analyses based on individual patient data make possible a more comprehensive analysis since all relevant data on a patient level are available. However, one limitation of the individual patient data approach is that researchers who wish to perform a meta-regression analysis often do not have access to the individual data. The usual unavailability and expense of collecting such data and the availability of summary data from published studies has led to the application of meta-regression for predicting summary treatment effects by summary patient statistics across studies. Regular use of this method would require a very high degree of collaboration.

We conclude from the present meta-regression that there is no evidence of relationship between BMD changes and reduction in risk of fracture among patients receiving calcium with or without vitamin D supplementation. The magnitude of the changes in spine or hip BMD does not explain the reductions in risk for fractures. It is likely that calcium, alone or in combination with vitamin D, have anti-fracture efficacy through a mechanism independent of bone density.

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Conflicts of interest No particular conflict of interest for this particular study. However, Véronique Rabenda, Olivier Bruyère, and Jean-Yves Reginster have received research grants and/or consulting fees from pharmaceutical companies.

References

1. Delmas PD (2002) Treatment of postmenopausal osteoporosis. Lancet 359:2018–2026
2. Temple RJ (1995) A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT (eds) Clinical measurement in drug evaluation. Wiley, New York
3. Li Z, Chines AA, Meredith MP (2004) Statistical validation of surrogate endpoints: is bone density a valid surrogate for fracture? J Musculoskelet Neuron Interact 4:6474
4. Bouxsein ML, Delmas PD (2008) Considerations for development of surrogate endpoints for antifracture efficacy of new treatments in osteoporosis: a perspective. J Bone Miner Res 23:1155–1167
5. Boonen S, Body JJ, Boutsen Y, Devogelaer JP, Goemaere S, Kaufman JM, Rozenberg S, Reginster JY (2005) Evidence-based guidelines for the treatment of postmenopausal osteoporosis: a consensus document of the Belgian Bone Club. Osteoporos Int 16:239–254
6. Rizzoli R, Boonen S, Brandi ML, Burlet N, Delmas P, Reginster JY (2008) The role of calcium and vitamin D in the management of osteoporosis. Bone 42:246–249
7. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A (2007) 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 370:657–666
8. Jadad AR, Moore RA, Carroll D, Jenkinson C (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12
9. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50:1088–1101
10. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple graphical test. BMJ 315:629–634
11. Hatal R, Keitz S, Wyer P, Guyatt G, on behalf of the Evidence-Based Medicine Teaching Tips Working Group (2005) Tips for learners of evidence-based medicine: 4. Assessing heterogeneity of primary studies in systematic reviews and whether to combine their results. CMAJ 172:661–665
12. Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ (1993) Effect of calcium supplementation on bone loss in postmenopausal women. N Engl J Med 328(7):460–464
13. Chevalley T, Rizzoli R, Nydegger V, Slosman D, Rapin CH, Michel JP, Vasey H, Bonjour JP (1994) Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. Osteoporos Int 4:245–252
14. Riggs BL, O'Fallon WM, Muhs J, O'Connor MK, Kumar R, Melton LJ 3rd (1998) Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. J Bone Miner Res 13:168–174
15. Peacock M, Liu G, Carey M, McClintock R, Ambrosius W, Hui S, Johnston CC (2000) Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. J Clin Endocrinol Metab 85:3011–3019
16. Fujita T, Ohue M, Fujii Y, Miyauchi A, Takagi Y (2004) Reappraisal of Katsuragi calcium study, a prospective, double-blind, placebo-controlled study of the effect of active absorbable algal calcium (AAACa) on vertebral deformity and fracture. J Bone Miner Metab 22(1):32–38
17. Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U, Bolland MJ, Gamble GD (2006) Randomized controlled trial of calcium in healthy older women. Am J Med 119:777–785
18. Prince RL, Devine A, Dhaliwal SS, Dick IM (2006) Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med 166:869–875
19. Reid IR, Ames R, Mason B, Reid HE, Bacon CJ, Bolland MJ, Gamble GD, Grey A, Horne A (2008) Randomized controlled trial of calcium supplementation in healthy, nonosteoporotic, older men. Arch Intern Med 168(20):2276–2282
20. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas P, Meunier PJ (1992) Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med 327:1637–1642
21. Dawson-Hughes B, Harris S, Krall E, Dallal G (1997) Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 337:670–676
22. Chapuy MC, Pamphile R, Paris E, Kempf C, Schlichting M, Arnaud S, Garnero P, Meunier PJ (2002) Combined calcium and vitamin D3 supplementation in elderly women:confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int 13:257–264
23. Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ (2004) A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: the Nottingham Neck of Femur (NoNOF). Study Age Ageing 33(1):45–51
24. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Women's Health Initiative Investigators et al (2006) Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 354:669–683
25. Bolton-Smith C, McMurdo ME, Paterson CR, Mole PA, Harvey JM, Fenton ST, Prynne CJ, Mishra GD, Shearer MJ (2007) Two-year randomized controlled trial of vitamin K1 (phylloquinone) and vitamin D3 plus calcium on the bone health of older women. J Bone Miner Res 22(4):509–519
26. Salovaara K, Tuppurainen M, Kärkkäinen M, Rikkonen T, Sandini L, Sirola J, Honkanen R, Alhava E, Kröger H (2010) Effect of vitamin D3 and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial—The OSTPRE-FPS. JBMR 25:1487–1495
27. Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD (2002) Relationships between bone mineral density and incident vertebral fractures with raloxifene therapy. J Bone Miner Res 17:1–10
28. Watts NB, Cooper C, Lindsay R et al (2004) Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. J Clin Densitom 7:255–261
29. Li Z, Meredith MP, Hoseyni MS (2001) A method to assess the proportion of treatment effect explained by a surrogate endpoint. Stat Med 20:3175–3188
30. Hochberg MC, Ross PD, Black D, Fracture Intervention Trial Research Group et al (1999) Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Arthritis Rheum 42:1246–1254
31. Bruyère O, Roux C, Badurski J et al (2007) Relationship between bone mineral density changes and fracture risk reduction in patients treated with strontium ranelate. J Clin Endocrinol Metab 23:3076–3081
32. Wasnich RD, Miller PD (2000) Antifracture efficacy with antiresorptive agents are related to changes in bone density. J Clin Endocrinol Metab 85:231–236
33. Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, Black DM (2002) Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. Am J Med 112:281–289
34. Hochberg MC, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD (2002) Changes in bone density and turnover

explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. J Clin Endocrinol Metab 87:1586–1592
35. Delmas PD, Seeman E (2004) Changes in bone mineral density explain little of the reduction in vertebral and nonvertebral fracture risk with anti-resorptive therapy. Bone 34:599–604
36. Bauer DC, Black DM, Garnero P, Hochberg M, Ott S, Orloff J, The Fracture Intervention Trial Study Group et al (2004) Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the fracture intervention trial. J Bone Miner Res 19:1250–1258
37. Compston J (2009) Monitoring osteoporosis treatment. Best Pract Res Clin Rheumatol 23:781–788
38. International Society for Clinical Densitometry. Official positions. Available at: www.iscd.org
39. National Osteoporosis Foundation. New clinicians guide to prevention and treatment of osteoporosis. Available at: www.nof.org
40. Thompson S, Higgins J (2002) How should meta-regression analyses be undertaken and interpreted? Stat Med 21:1559–1573
41. Lambert P, Sutton A, Abrams F et al (2002) A comparison of summary patient-level covariates in meta-regression with individual patient data meta-analysis. J Clin Epidemiol 55:86–94