

CORRESPONDENCE



Calcium plus Vitamin D and the Risk of Fractures

TO THE EDITOR: The increased incidence of nephrolithiasis among patients taking supplemental calcium carbonate that was reported by Jackson et al. (Feb. 16 issue)¹ might have been avoided if calcium citrate had been given. It has been shown that urinary calcium oxalate crystals that form in the presence of hypercalciuria and hyperoxaluria develop into clinically important stones only after aggregation into larger particles. This aggregation is inhibited by citrate at physiologic concentrations.^{2,3}

The data in Table 3 in the report suggest that calcium and vitamin D reduced the incidence of hip fracture more in older patients than in younger patients, which is not unexpected, given the pathophysiological differences between perimenopausal bone loss and senile bone loss.⁴ Measurement of parathyroid hormone levels to assess the adequacy of vitamin D intake might have helped in the interpretation of these findings.^{5,6} The dose of supplementary vitamin D used in this study, assuming it was the sole or major source of vitamin D, may have been too low to have had a more dramatic effect in either age group.

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1. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669-83. [Erratum, *N Engl J Med* 2006;354:1102.]
2. Glauser A, Hochreiter W, Jaeger P, Hess B. Determinants of urinary excretion of Tamm-Horsfall protein in non-selected kidney stone formers and healthy subjects. *Nephrol Dial Transplant* 2000;15:1580-7.
3. Hess B, Jordi S, Zipperle L, Ettinger E, Giovanoli R. Citrate determines calcium oxalate crystallization kinetics and crystal morphology — studies in the presence of Tamm-Horsfall protein of a healthy subject and a severely recurrent calcium stone former. *Nephrol Dial Transplant* 2000;15:366-74.
4. Riggs BL. Overview of osteoporosis. *West J Med* 1991;154:63-77.
5. Kinyamu HK, Gallagher JC, Rafferty KA, Balhorn KE. Die-

tary calcium and vitamin D intake in elderly women: effect on serum parathyroid hormone and vitamin D metabolites. *Am J Clin Nutr* 1998;67:342-8.

6. Holick MF, Siris ES, Binkley N, et al. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab* 2005;90:3215-24.

TO THE EDITOR: Although Jackson and coworkers conclude that calcium and vitamin D supplementation did not significantly reduce fracture rates among women 50 to 79 years of age, their observations can be interpreted to provide support for a different conclusion. Since it has been well established that bone mineral density (BMD) decreases progressively in postmenopausal women who are not treated for bone loss, one is struck by the authors' finding that the mean BMD for the total spine and the whole body in the control subjects increased steadily over the nine years of the study, and that the BMD for the total hip remained essentially unchanged, as shown in Figure 2 of the article by Jackson et al. This phenomenon was almost surely influenced by the large proportion of control subjects who were already taking cal-

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cium or vitamin D at “therapeutic” doses. One would expect improved BMD to be associated with fewer fractures; the investigators did, in fact, find fracture rates for both control subjects and treated subjects to be less than half the rate historically anticipated. It is also not surprising that the administration of additional calcium and vitamin D to treated subjects further reduced hip fractures only to a limited degree, particularly since the optimal intakes of both are unknown.

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TO THE EDITOR: The results of the Women’s Health Initiative (WHI) trial of calcium with vitamin D reveal that calcium and vitamin D supplementation (1000 mg of calcium carbonate with 400 IU of vitamin D) did not lower fracture rates but did increase the risk of kidney stones in calcium-replete postmenopausal women (mean intake, 1150 mg per day) whose intake of vitamin D was insufficient (serum 25-hydroxyvitamin D, 48 nmol per liter). How should these results influence clinical practice? They should have no effect on the evidence-based recommendation that postmenopausal women, who typically consume 600 mg of elemental calcium per day, should increase their calcium intake to 1200 mg per day.¹ Similarly, the results should not deter physicians from recommending 800 IU of vitamin D per day — the amount the average postmenopausal woman needs to raise her serum 25-hydroxyvitamin D level to that needed to lower the risk of fracture (≥ 75 nmol per liter).² Finally, the increased risk of kidney stones among the women in the study who were consuming a mean of 2150 mg per day of calcium (usual mean intake plus supplement), as compared with those consuming 1150 mg per day, should not be assumed to apply to women who increase their intake to 1200 mg per day. It is important that the WHI trial not be used to sanction the inadequate intake of calcium and vitamin D that is so widespread among postmenopausal women today.

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Dr. Dawson-Hughes reports having received an honorarium from GlaxoSmithKline.

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes: for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, D.C.: National Academy Press, 1997.
2. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporos Int* 2005;16:713-6.

THE AUTHORS REPLY: Dr. Terris notes that use of supplemental calcium citrate, instead of calcium carbonate, may lessen the risk of kidney stones observed in the WHI calcium with vitamin D trial, and we agree. However, calcium carbonate, perhaps because of its greater affordability, is still the most common form of calcium supplementation used in the United States. The present study did not have the power to examine changes in parathyroid hormone levels among women with hip fracture and controls, because stored specimens were available after randomization for a subsample of the trial population that consisted of only 6 percent of the subjects.

Dr. Lesser attributes the low rate of hip fracture in the placebo group to the already high levels of calcium intake at baseline. As we report, there are other powerful fracture-lowering factors that probably also contributed, including high levels of hormone use and body-mass index and the enrollment of fewer women over 70 years of age than expected. Nonetheless, we believe that the trial results provide several indications that calcium intake does reduce the risk of hip fracture. Calcium and vitamin D supplementation reduced the risk of hip fracture by 29 percent among women with an adherence of 80 percent or more, 21 percent among those 60 years of age or older at enrollment, and 30 percent among those not taking other calcium supplements during the trial (all 95 percent confidence intervals for the corresponding hazard ratios exclude 1). In fact, we believe that these data support current recommendations for adequate calcium intake.

Two other clarifications are important to make in the interpretation of the trial results. First, the increased risk of kidney stones was not associated with high baseline calcium intake. Our preliminary analyses indicated no interaction with baseline calcium intake and, in fact, a somewhat greater risk among women with a lower total calcium intake at baseline. The factors contributing to an increase in the risk of kidney stones are under investigation. Second, some have disregarded the greater effects of the calcium-plus-

vitamin-D intervention in older women as being uninterpretable, claiming that the randomization was no longer intact in subgroups defined according to age. In fact, the randomization of women in all the WHI trials was stratified according to age in order to ensure that measured and unmeasured characteristics would be balanced within the age groups. There are other caveats associated with subgroup analysis (e.g., multiple comparisons and lack of power), but in the WHI

trials, age-specific analyses are protected from confounding by the randomized design.

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for the Women's Health Initiative Investigators

Calcium plus Vitamin D and the Risk of Colorectal Cancer

TO THE EDITOR: The findings of the Women's Health Initiative (WHI) trial of calcium and vitamin D supplementation and the risk of colorectal cancer reported by Wactawski-Wende et al. (Feb. 16 issue)¹ are not surprising. The chief problem with the study, in retrospect, is that, as the authors acknowledge, the dose of 400 IU of vitamin D₃ was inadequate to raise blood levels of 25-hydroxyvitamin D to what is now considered a healthful range above 78 nmol per liter (30 ng per milliliter). It is now generally recommended that 1000 IU of vitamin D₃ per day is necessary to attain this level² and to maximize intestinal absorption of calcium³ for optimal bone health and the prevention of cancer.⁴ Virtually all the subjects in the study had vitamin D insufficiency according to the criterion given above, both at the beginning and at the end of the trial. The most important finding of this study is that women in the lowest quartile of serum 25-hydroxyvitamin D levels (less than 31 nmol per liter) had an incidence of colorectal cancer that was 253 percent of the incidence in the highest quartile (serum 25-hydroxyvitamin D level, \geq 58.4 nmol per liter). These data are consistent with the observation that there was an inverse relationship between serum 25-hydroxyvitamin D levels and the risk of colon cancer.^{5,6} These women needed more vitamin D.

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1. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006;354:684-96. [Erratum, *N Engl J Med* 2006;354:1102.]

2. Tangpricha V, Koutkia P, Rieke SM, Chen TC, Perez AA,

Holick MF. Fortification of orange juice with vitamin D: a novel approach to enhance vitamin D nutritional health. *Am J Clin Nutr* 2003;77:1478-83.

3. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *J Am Coll Nutr* 2003;22:142-6.

4. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* 2004;80:Suppl:1678S-1688S.

5. Gorham ED, Garland CF, Garland FC, et al. Vitamin D and prevention of colorectal cancer. *J Steroid Biochem Mol Biol* 2005;97:179-94.

6. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer* 2002;94:1867-75.

TO THE EDITOR: The findings from the WHI trial with regard to colorectal cancer appear to be in contrast to epidemiologic data. Two critical issues are the dose and the duration of treatment. On the basis of the association between plasma 25-hydroxyvitamin D and colorectal cancer in the Nurses' Health Study (NHS),¹ the calculated risk reduction for the intervention in the WHI trial would be only about 13 percent. Moreover, in the NHS, a statistically significant reduction in colorectal cancer in association with a higher intake of vitamin D emerged only among women who used supplements for more than 10 years.² In randomized trials, calcium reduces the recurrence of adenoma, including that of large adenomas, consistent with a role of calcium in early stages of carcinogenesis.³ Epidemiologic data suggest that the benefits of calcium may level off at a dose of approximately 700 mg per day.⁴ In the WHI trial, the calcium intake was 1151 mg per day at baseline and was reported to increase during the trial. It is unclear how many women were consuming calcium at a dose low enough to benefit from the intervention, or whether the duration of the in-