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COMMENTARIES

Calcium, Vitamin D, and Fractures in the WHI Data

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Commentary on: Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SA, Black HR, Blanchette P, Bonds DE, Brunner RL, Brzyski RG, Caan B, Cauley JA, Chlebowski RT, Cummings SR, Granek I, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Johnson KC, Judd H, Kotchen JM, Kuller LH, Langer RD, Lasser NL, Limacher MC, Ludlam S, Manson JE, Margolis KL, McGowan J, Ockene JK, O'Sullivan MJ, Phillips L, Prentice RL, Sarto GE, Stefanick ML, Van Horn L, Wactawski-Wende J, Whitlock E, Anderson GL, Assaf AR, Barad D; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med.* 2006 Feb 16;354(7):669-83.

There was great hope that the Women's Health Initiative (WHI) would lay to rest several clinical questions still in dispute. Here we offer some observations about the anti-fracture efficacy of supplemental calcium (Ca) and vitamin D recently reported by the WHI (1). The abstract states that these interventions "did not significantly reduce hip fracture" among postmenopausal women. With few exceptions (2), the popular media overlooked the subtleties of this study, leaving the public to suspect that Ca and vitamin D are two more discounted myths. Those who did read the fine print could discern that the data did not shed very much light on the clinical question. *In fact, we believe that the limitations of this study all but negate its validity.*

The Subjects at Entry

The 36,000+ women who were randomized for this study were recruited from two other WHI trials (Dietary Modification and Hormone Therapy). At entry, ~22% had already been assigned to active hormone therapy; others were allowed to take HRT on their own. Altogether, 52% of the subjects were on estrogen.

Other anti-osteoporosis treatments (*e.g.*, calcitonin or bisphosphonates) were also allowed. At entry, only 1% of the participants were taking these treatments (but that changed during the study).

The subjects were also allowed to take supplemental Ca (up to 1000 mg/d) and/or vitamin D (up to 1000 IU/d) on their own, regardless of whether they were allocated to the Ca+D group or the placebo group. At entry, the estimated mean total Ca intake from supplements, diet, and medications was 1100 to 1200 mg/d; this figure was <800 mg/d in only 33% and <400 mg/d in only 7% of the subjects. Mean vitamin D intake (from supplements and diet) was ~370 IU/d.

Body weight was <58 kg in <10% of the women, and BMI was <25 in only ~26% of the women. The remainder of the women could be categorized by BMI as either overweight (~35%) or frankly obese (~37%). We note that the paper repeatedly identifies the subjects as "*healthy* postmenopausal women" (emphasis added).

At entry, hip T-score was above -1 in ~60% of the subset of participants (15%) who had DXA scans.

The Study Itself

The subjects were randomly assigned to the Ca+D (Ca 1000 mg/d plus vitamin D_3 400 IU/d, to be taken in divided doses with

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meals) or placebo groups. They were followed by periodic visits to ascertain adherence and outcome measures for a mean of 7y.

During participation in the study >15% of the subjects used anti-osteoporosis drugs, principally bisphosphonates.

The investigators defined subjects as adherent if they used at least 80% of study tablets during an observation interval. Mean adherence was ~60% throughout the trial. By the end, however, 24% of the subjects were no longer taking *any* study tablets.

The observed annual rate of hip fracture (16/10,000) was less than half that predicted in the trial design (34/10,000).

Findings

In intention-to-treat analysis, Ca and vitamin D reduced the risk of hip fracture by 12% (hazard ratio, 0.88), but the finding was not significant (95% CI, 0.72 to 1.08). *However in per-protocol analysis (limited to adherent subjects), the risk of hip fracture was reduced by 29% (hazard ratio 0.71), and the finding was significant (95% CI, 0.52 to 0.97).*

Osteoporosis Briefly Revisited

Fractures occur when the force encountered by bone overcomes its strength. Some loss of bone strength with aging is inevitable (3). However, in osteoporosis, the skeleton becomes fragile enough that fractures become common; in many older patients, this situation is worsened by a propensity to fall. The mix of problems that leads to osteoporosis varies from patient to patient, including genetic predisposition, poor nutrition, poor vitamin D status, low body weight, physical inactivity, estrogen deficiency, cigarette smoking, alcohol abuse, co-morbidities, drugs, and so on. We think that it is unusual that just one or two of these problems bear *full responsibility* for a patient's osteoporosis. It appears that the final common pathway, however, is elevated activation frequency, the tissue-level mechanism by which bone is lost and its intrinsic resistance to fracture is compromised (4;5).

Were These Women at Risk for Osteoporosis?

Although a huge effort must have been expended to carry out this arm of the WHI, one must wonder what fraction of participants were in a position to derive skeletal benefit from the intervention.

Most of the participants in this trial were probably at low risk for osteoporotic fractures by some combination of the following: high BMI, estrogen replacement, adequate Ca intake, and normal hip T-score. A significant subset of participants were also taking bisphosphonates during the trial.

Ca seems to be a threshold nutrient; beyond a certain intake, benefit tends to level off (6;7). The baseline Ca intake of most subjects was probably near or above that threshold, leaving little or no room for benefit *and effectively eliminating an untreated placebo group for Ca* (8).

Vitamin D status was probably suboptimal in most participants; mean baseline levels for 25(OH)D were <50 nmol/L. It has been shown that a 25(OH)D level of at least 80 nmol/L is required for full therapeutic benefit, and one can safely predict that a supplement of 400 IU/d would fail to raise subjects' values to this level (9;10). Most clinicians now include a vitamin D_3 supplement of at least 1000 IU/d in regimens for prevention (and treatment) of osteoporosis.

Perhaps the RCT is not the right tool for evaluating nutritional interventions (8).

Conflict of Interest: The authors have declared that no conflicts of interest exist.

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