

# A Matter of PERSPECTIVE

*The viewpoints expressed in "A Matter of Perspective" are those of the contributors, and not necessarily those of Menopause Management or The North American Menopause Society (NAMS).*

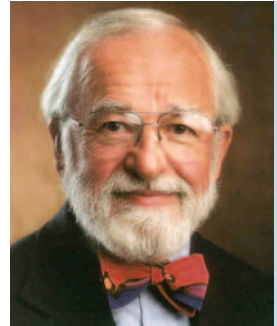
## The WHI Report on Calcium and Vitamin D Supplementation: Good News, Not Bad News

Leon Speroff, MD

Do you remember when you first heard about the calcium/vitamin D results from the Women's Health Initiative (WHI)? I was watching NBC news prior to the Olympics telecast. The next day I heard it on National Public Radio, and later I read it in *Newsweek*. All the presentations said the same thing: New study produces disappointing news, challenging long-held beliefs; no benefit for calcium/vitamin D supplementation. This was a typical demonstration of the guiding principle for the media: good news is no news. But who is to blame: the media or the WHI investigators? Let's first consider the study itself and the interpretation provided by the WHI investigators.

### THE WHI Interpretation

The WHI conducted a randomized trial of calcium and vitamin D supplementation,<sup>1</sup> which involved 36,282 postmenopausal women who were part of the WHI clinical trials of postmenopausal hormone therapy (HT) or dietary modification. The average follow-up was 7 years. Thirty-seven percent of the women were 50 to 59 years of age, 45.5% were 60 to 59, and 17.5% were 70 to 79. The treated group received 1,000-mg calcium and 400-IU vitamin D supplementation daily. Most of the women were overweight, with 37% having a body mass index of 30 or higher.



Leon Speroff, MD

A subset of 1,431 women was given bone density measurements and was followed for 6 years. There were no bone density differences between the treatment and placebo groups in the spine or whole body measurements, but the treated group gained slightly more bone density in the hip at year 3, and by year 6 the placebo group had lost more bone at the hip. Fracture results are in the Table below.

#### Table.

	Calcium/Vitamin D	Placebo	HR (CI)*
<b>Intention-to-Treat Analysis</b>			
Hip fractures	175	199	0.88 (0.72 - 1.08)
Vertebral fractures	181	197	0.90 (0.74 - 1.10)
<b>Analysis of Adherent Participants<sup>†</sup></b>			
Hip fractures	68	99	0.71 (0.52 - 0.97)
Vertebral fractures	91	104	0.89 (0.67 - 1.19)

\*HR= hazard ratio, CI=confidence interval

<sup>†</sup>Analysis corrected for compliance by analyzing only those women who continued their treatment.

The WHI emphasized the finding that the overall analysis indicated no significant reduction in fractures with calcium/vitamin D treatment, and that the women treated with calcium/vitamin D had a 17% greater risk of kidney

stones (HR = 1.17, CI = 1.02-1.34). This was the news reported by the media.

### A Different Point of View

The WHI investigators chose to ignore the good results and emphasize the negative aspects of the findings. A careful reading of the full WHI report reveals important, good news that was not reported in the media:

1. Correcting for compliance by analyzing only those women who continued their treatment revealed a statistically significant, 29% reduction in the risk for hip fractures. At the end of the trial only 59% of the treated women were taking the intended dose of calcium and vitamin D. (It should be noted that a placebo-controlled, 5-year clinical trial in Australia<sup>2</sup> recently reported a 34% [significant] reduction in all fractures in an elderly population compliant with calcium supplementation; at the same time, no overall effect was seen because only 57% of the women took 80% or more of their assigned medication.)
2. Women who were age 60 and older had a significant, 21% reduction in hip fractures (HR = 0.79, CI = 0.64-0.98).
3. The reduction in hip fractures was greater in those women who were not taking calcium supplements other than what the study provided.
4. The reduction in hip fractures was greatest (42%) in those women who combined calcium/vitamin D supplementation with postmenopausal HT (HR = 0.58, CI = 0.37-0.93).

In my view, the public presentation of the results of the WHI calcium/vitamin D study was not accurate. It wasn't explained that the women in this study were not at high risk for fractures, or that the population at greatest risk for fractures (the oldest women in the study) actually *benefited* from the therapy. Indeed, whole-body and spinal bone density increased in the placebo group. This is hard to explain; the average untreated postmenopausal woman loses spinal bone density. In this study, only hip bone density demonstrated a loss, and thus it is not surprising that significant benefits were demonstrated only with regard to hip fractures.

The fact that most of these women were overweight probably contributed to the protection against bone loss in the spine. In addition, the average calcium intake of the women in the WHI study (including those in the placebo group) was relatively high, also contributing to the findings in the placebo group. In a population of women losing bone density in both hip and spine, and in women with other risk factors for fractures, I would expect calcium/vitamin D supplementation to yield even better results than those reported by the WHI, including a reduction in spinal and arm fractures.

*In my view, the public presentation of the results of the WHI calcium/vitamin D study was not accurate. It wasn't explained that the women in this study were not at high risk for fractures, or that the population at greatest risk for fractures (the oldest women in the study) actually benefited from the therapy.*

Contrary to the presentation in the media, the news in this WHI report was actually good. The women who most needed a benefit experienced a reduction in hip fractures with calcium/vitamin D if they continued to supplement their dietary intake. The results also further support what was already known—that maximal protection against fractures is gained by combining calcium/vitamin D supplementation with HT. Because the average woman gets only about 500 mg of calcium in her daily diet, most women not taking HT require a daily supplement of 1,000 mg calcium (best as single doses of 500 mg with meals). Most women taking HT require only an additional 500 mg of calcium because estrogen improves calcium absorption.

### Colorectal Cancer

The WHI study also assessed the impact of calcium/vitamin D on the risk of invasive colorectal cancer.<sup>3</sup> No difference was observed between the treated group and the placebo group, even when only women adherent to treatment were analyzed. However, it is recognized that the la-

*The impact of calcium/vitamin D supplementation on the risk of colorectal cancer remains unsettled. A reduction in colorectal cancer is still possible in those women who have low levels of calcium and vitamin D prior to treatment...*

tency period for colorectal cancer is 10 to 20 years. The length of follow-up in this study may have been insufficient to detect an effect. Furthermore, colorectal cancer was not a primary outcome in the study design, and the study design was very much complicated by the fact that the women were simultaneously enrolled in three overlapping trials (calcium/vitamin D, low-fat diet, and HT).

The impact of calcium/vitamin D supplementation on the risk of colorectal cancer remains unsettled. A reduction in colorectal cancer is still possible in those women who have low levels of calcium and vitamin D prior to treatment, as documented in the Nurses' Health Study, and in the current WHI report (if you examine the report closely).<sup>3,4</sup> In other words, the WHI data did indicate a decreasing risk of colorectal cancer as serum levels of 25-hydroxyvitamin D increased.

### Kidney Stones

What about the WHI's findings of an increased risk of kidney stones in women taking calcium/vitamin D supplementation? The women in this trial were allowed to continue their own programs of supplementation.

Thus, many took calcium and multivitamins (which contain 400 IU vitamin D). The average daily calcium intake of the study population was 1,100 to 1,200 mg—twofold higher than the average American woman. The WHI does not provide data to answer this most important question: Was the small increase in kidney stones observed in women who were taking excessive amounts of calcium and vitamin D?

### More Aggressive Treatment

The prevalence and importance of vitamin D deficiency has received new attention, leading to more aggressive guidelines.<sup>5</sup> A group of bone experts reached a consensus by considering the amount of vitamin D supplementation required to change blood levels of 25-hydroxyvitamin D and parathyroid hormone, correlating this information with the levels of vitamin D required to prevent bone loss.<sup>5</sup> The optimal serum level of 25-hydroxyvitamin D is greater than 30 ng/mL. To reach this level, it was recommended that men and women, 60 years of age and older, need a daily supplement of 800 to 1,000 IU of vitamin D<sub>3</sub>. Some bone experts are treating patients with 50,000 IU vitamin D<sub>2</sub>, administered only once a month, with a product that requires a prescription. With this regimen, the vitamin D is stored and made available on a consistent basis over time. To be sure, there are some women who derive sufficient amounts of calcium from their diets, and supplementation in these women would be unnecessary, and would perhaps put them at risk for kidney stones. Toxic effects with vitamin D, however, require doses far beyond those currently recommended. New preparations are now needed to satisfy the new recommendations. Multivitamins contain only 400 IU of vitamin D<sub>3</sub>, and excessive intake of the vitamin A component of the multivitamin has been reported to be associated with an increased rate of hip fractures.<sup>6</sup>

These new recommendations indicate that clinicians should be more aggressive in monitoring serum levels of 25-hydroxyvitamin D. It is argued that this measurement should be

*(continued on page 39)*

The *2006 Recognition Awards* booklet will soon be printed and also posted on the NAMS Web site, as both NAMS members and non-members may submit nominations. Completed nomination forms are due by July 30.

may earn up to 4 hours of Category 1 CME credits. The request for CME is \$25, but NAMS members may participate at no charge. The slide set is also available. Access this course at: [www.obgyn.net/nams-menopause-basics-cme/](http://www.obgyn.net/nams-menopause-basics-cme/).

### “Menopause Basics 2006” as Webcast

To reach a larger professional audience with much-needed information, the popular half-day NAMS course presented prior to past Annual Meetings has been formatted as a Webcast on the OBGYN.net Web site for the entire year. Content is approved by the NAMS Board and presented by experts in the field: Margery L.S. Gass, MD; Jennifer L. Prouty, MSN, NP, CS; and Wulf H. Utian, MD, PhD. “Menopause Basics 2006” offers a comprehensive overview, including terminology, physiology, patient evaluation, treatment options for menopause symptoms, preventing chronic disease later in life, and counseling tips. Participants

### Sit the Exam This October: Your Patients Deserve the Best!

“If you’re not currently a NAMS Menopause Practitioner, you are invited to sit the exam,” said Elizabeth Contestabile, RNC, BScN, Chair of the 2005-2006 Exam Committee. “It’s offered next on October 11, 2006, just prior to the NAMS Annual Meeting in Nashville, TN.”

The registration deadline is August 2 (late application deadline is September 2, requiring an additional \$75 processing fee). Complete information, including the registration application, is available in the *2006 Candidate Handbook* found on the NAMS Web site ([www.menopause.org/compexam.htm](http://www.menopause.org/compexam.htm)). ■

### A Matter of Perspective

(continued from page 26)

part of every older individual’s annual medical assessment. The dose of vitamin D<sub>3</sub> supplementation can be easily titrated according to the circulating vitamin D level. In addition, patients who lose bone despite adequate treatment for bone loss should have this serum measurement performed because inadequate calcium and vitamin D can be the reason for the loss.

### It’s Not the Media

We are quick to castigate the media for melodramatic reports of adverse or disappointing study results. But it is time to focus on the manner in which information is provided to the media. Knowing that sentences and data are quoted in sound bites, efforts should be made to produce manuscripts, press releases and interviews that are accurate and balanced. ■

Leon Speroff, MD, is Professor of Obstetrics and Gynecology at Oregon Health & Sciences University, Portland, OR.

Dr. Speroff has received grants and research support from Wyeth Pharmaceuticals and Organon USA, and he is a consultant for Warner Chilcott PLC.

Submitted: April 20, 2006. Accepted May 2, 2006.

Send your contributions to “A Matter of Perspective” to the managing editor, Jackie Syrop, at [jsyrop@menopausegmt.com](mailto:jsyrop@menopausegmt.com). We will edit articles for style and space requirements. Authors will have final approval of the articles prior to publication.

### References

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.
2. Prince RL, Devine A, Dhaliwal SS, et al. 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* 2006; 166:869-75.
3. 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.
4. Feskanich D, Ma J, Fuchs CS, et al. Plasma vitamin D metabolites and risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev* 2004;13:1502-08.
5. Dawson-Hughes B, Heaney RP, Holick MF, et al. Estimates of optimal vitamin D status. *Osteoporosis Int* 2005;16:713-16.
6. Feskanich D, Singh V, Willett WC, et al. Vitamin A intake and hip fractures among postmenopausal women. *JAMA* 2002;287:47-54.