

High Vitamin D Doses Lower Fracture Risk for Most Vulnerable

Diedra Henderson

July 04, 2012

July 4, 2012 — Those older than 65 years who take high doses of vitamin D lower their risk of suffering a fracture by from 14% to 30%, according to a pooled analysis that demonstrated fracture risk reduction only at the highest level of vitamin D intake.

Heike A. Bischoff-Ferrari, MD, DrPH, from the Center on Aging and Mobility at the University of Zurich and the Wald City Hospital, Zurich, Switzerland, and coauthors reported their findings in a study published online July 4 and in the July 5 print edition of the *New England Journal of Medicine*.

"The findings suggest that only a high intake of vitamin D [median, 800 IU daily; range, 792 - 2000 IU] leads to a significant reduction in the risk of fracture — with a 30% reduction in the risk of hip fracture [hazard ratio, 0.70; 95 percent confidence interval (CI), 0.58 - 0.86; $P < .001$] and a 14% reduction in the risk of any nonvertebral fracture [hazard ratio, 0.86; 95% CI, 0.76 - 0.96; $P = .007$]; this reduction is independent of the assigned treatment dose of vitamin D, age group, sex, type of dwelling, and study," the authors write.

Dr. Bischoff-Ferrari and coauthors sought to shed light on the relationship between supplemental vitamin D and reduced fracture risk; a simple question that has bedeviled scores of research teams, with several meta-analyses and 1 prior pooled participant-level analysis yielding inconsistent results. About 75% of fractures are suffered by people aged 65 years or older.

The research team identified all double-blind, randomized controlled trials involving people aged 65 years and older that evaluated oral vitamin D supplements (taken by themselves or in combination with calcium) compared with placebo or calcium alone, which included data on low-trauma fractures and were published on or before August 31, 2011.

Eleven of the 12 studies included source data for 30,011 participants, including type and date of fracture and the dates participants entered and left the study. For 11 studies, which included 31,022 people, participants took vitamin D daily, weekly, or every 4 months. Vitamin D supplementation outside of the formal study was permitted in 5 of 11 trials. Data on the sex of participants and their type of dwelling were available for all 12 studies. The end points of interest were hip fracture and nonvertebral fracture risks.

After establishing homogeneity among the 11 individual trials for both end points overall, as well as at the actual vitamin D intake level, the research team pooled the individual participant-level data and used Cox proportional-hazards regression analysis to assess the incidence of hip fracture or any nonvertebral fracture.

"The intention-to-treat analysis showed a nonsignificant 10% reduction in the risk of hip fracture (hazard ratio, 0.90; 95% [CI], 0.80 to 1.01)," the authors write. The primary comparison of actual intake, however, showed a significant reduction in hip fractures among participants taking the highest levels of vitamin D, which was confirmed by internal validation analysis.

Ethel S. Siris, MD, the Madeline C. Stabile Professor of Clinical Medicine at Columbia University and director of Columbia University's Toni Stabile Osteoporosis Center, New York City, told *Medscape Medical News* she was happy to see the study's results.

"There's been a lot of arguing back and forth about the role of vitamin D," Dr. Siris said. "There are different groups who are coalescing around the same ballpark, they're just not sitting in the same seats."

Dr. Siris said many have believed for years that diet alone does not provide enough vitamin D through consumption of food items that either naturally contain or are fortified with the nutrient, such as oily fish, milk, cereal, and orange juice. Younger people can drink in vitamin D when sunshine warms their skin, she said, but older people slathering on sunscreen to prevent melanoma are less able to make the vitamin.

The research group's finding is consistent with the prevailing theory that at least 800 IU vitamin D are needed per day to see even modest fracture prevention. In the real world, where bones are not perfect and patients forget to take pills, Dr. Siris says they advise patients to take at least 1000 to 2000 IU vitamin D daily "just to be sure."

In addition, Dr. Bischoff-Ferrari's research team reports that their subgroup analyses suggest that at the highest actual intake level (792 - 2000 IU per day), the risk for hip fracture is reduced among all people aged 65 years or older, whether they live in the community or in an institution (hazard ratio, 0.70; 95 CI, 0.58 - 0.86; $P < .001$). This runs counter to previous meta-analyses that suggested that only older people residing in institutions benefited from vitamin D supplementation.

Similarly, the researchers' pooled analysis of the 8 double-blind, randomized, controlled trials that used vitamin D combined with calcium indicated that with combined supplementation, fracture risk is reduced only at the highest actual intake of vitamin D. Several previous studies had dismissed the importance of the vitamin D dose when participants take it in combination with calcium.

In an accompanying editorial, Robert P. Heaney, MD, from the Osteoporosis Research Center, Creighton University Medical Center, Omaha, Nebraska, writes that previous inconsistent study results may be a result of researchers' failure to consider the dose-response relation that vitamin D shares with most nutrients. Taking vitamin D at levels that are too low "to push a person with a deficiency up onto the ascending limb of the response curve," Dr. Heaney writes, "is likely to produce a null response."

"The question of how much vitamin D is enough is likely to remain muddled as long as meta-analyses focus on trial methodology, rather than on biology," Dr. Heaney writes.

Although Dr. Bischoff-Ferrari and colleagues' study findings are strengthened by the large sample size, assessing fracture risk by actual vitamin D intake and confirmation of the primary findings by an internal validation study, the study has a number of limitations. For example, source data were not available for 2 of the 14 qualifying trials, and the researchers could not assess the effect of the highest quartile of actual vitamin D intake without additional calcium because all of the trials that gave vitamin D doses in excess of 800 IU daily also gave participants calcium. In addition, the threshold assessment of fracture was limited because baseline levels of 25-hydroxyvitamin D were available only for a subset of patients.

"[I]t would be important for future studies to consider the possibility that a calcium-supplement intake of 1000 mg per day or more, combined with high-dose vitamin D (≥ 800 IU per day) may be harmful," the authors conclude. "Calcium supplements without vitamin D have been reported to increase the risk of hip fracture."

The Swiss National Foundations, the European Commission, and DSM Nutritional Products supported this study. Dr. Bischoff-Ferrari disclosed financial relationships with Amgen, DSM, MSD, Nestle, Novartis and Roche. One of the study authors was a consultant for Cytochroma, Pfizer, and Servier. One study author was a paid member of the Meda Inc advisory board, received travel support from Meda, was a paid member of the Merck board, a paid consultant for Merck and a paid member of Merck's speakers' bureau. One author was a paid member of sanofi-aventis' speakers bureau. One study author was a paid consultant for Roche. The other authors and Dr. Siris have disclosed no relevant financial relationships. Dr. Heaney was a paid member of the National Dairy Council speakers bureau, received payment from the Council for Responsible Nutrition for manuscript preparation and payment from the Coca-Cola Co for developing educational presentations.

N Engl J Med. Published online July 4, 2012.

Medscape Medical News © 2012 WebMD, LLC

Send comments and news tips to news@medscape.net.

Cite this article: High Vitamin D Doses Lower Fracture Risk for Most Vulnerable - *Medscape* - Jul 04, 2012.