Annual High-Dose Vit. D Ups Fall, Fracture Risks

BY MARY ANN MOON

FROM JAMA

Far from protecting older women from falls and fractures, once-yearly high-dose oral vitamin D raised the risk of falls by 15% and that of fractures by 26%, according to a study by researchers in Australia.

As this study used the "largest total annual dose of vitamin D (500,000 IU) reported in any large randomized controlled trial," it is possible that these adverse outcomes are related to the dosage, or perhaps to the once-a-year regimen. But the levels of 25-hydroxycholecalciferol achieved in these subjects can also occur with other dosing regimens, so it appears that the safety of all high-dose vitamin D supplementation warrants further examination, said Kerrie M. Sanders, Ph.D., of the University of Melbourne and her associates.

Dr. Sanders and her colleagues performed their single-center study in 2,256 white women aged 70 and older who resided in southern Victoria. They were considered at risk for hip fracture because of their family or personal histories or because they reported recent falls.

The subjects were randomly assigned to receive a single oral dose of vitamin D (cholecalciferol) or a matching placebo at the same time every year for 3-5 years. Lab studies in a subgroup of the subjects showed that the active treatment raised levels of 25-hydroxycholecalciferol an average of 41%, as expected.

There were 5,404 falls during follow-up, involving 74% of the women taking vitamin D and 68% of those taking placebo. The rate of falls was 83 per 100 person-years with vitamin D, compared with 73 per 100 person-years with placebo, a statistically significant difference.

The increase in falls with active treatment was noted in falls that produced fractures, falls that did not produce fractures, and falls that produced soft-tissue injury. The percentage of falls requiring a physician's visit was similar between the two groups of subjects, at approximately 27% in both.

A total of 155 women taking vitamin D sustained 171 fractures during follow-up, compared with 125 women taking placebo who sustained 135 fractures. This translates to a rate of 4.9 fractures per 100 person-years with active treatment and 3.9 fractures per 100 person-years with placebo. These risks did not change after the data were adjusted to account for subjects' calcium intake.

"Contrary to our hypothesis, participants receiving annual high-dose oral cholecalciferol experienced 15% more falls and 26% more fractures than [did] the placebo group. Women not only experienced excess fractures after more frequent falls but also experienced more fractures that were not associated with a fall," the investigators noted (JAMA 2010;303:1815-22).

"A post hoc analysis found that the increased likelihood of falls in the vitamin D group was exacerbated in the 3-month period immediately following the annual dose, and a similar temporal trend was observed for fractures," they added.

In an accompanying editorial, Dr. Bess Dawson-Hughes and Susan S. Harris, D.Sc., of the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, said that these study findings should not detract from the importance of "correcting widespread vitamin D deficiency and insufficiency. "There is no evidence for adverse effects of more frequent, lower-dose regimens, so daily, weekly, or monthly dosing with vitamin D_3 appears to be the best option for clinicians at this time," they noted (JAMA 2010;303:1861-2).

Dr. Dawson-Hughes and Dr. Harris also explored possible explanations for the study's surprising results. It may be that the single large dose of vitamin D triggered a short-term "protective" reaction in which the enzyme that catabolizes it was upregulated, "resulting in decreased blood and tissue levels of 1,25-dihydroxyvitamin D." This dropoff may have, in turn, raised the risk of falls and fractures. Alternatively, some as-yet unknown benefit of vitamin D therapy may have had the unintended effect of raising fall and fracture risks. For example, the treatment may have improved physical performance, reduced chronic pain, or improved mood, any of which could lead to increased activity and thereby increased chances for falling. ■

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BMD Mostly Recovers After Cessation of Depo-Provera

BY DEBRA L. BECK

FROM THE ANNUAL MEETING OF THE SOCIETY FOR ADOLESCENT HEALTH AND MEDICINE

TORONTO — Bone mineral density loss in female adolescents receiving depot medroxyprogesterone acetate for contraception was substantially or fully reversible following discontinuation of the drug, according to study results.

In girls who lost more than 5% of bone mineral density (BMD) during treatment, however, complete recovery was less likely. Also, recovery was generally greater and faster in the lumbar spine than the hip.

"If someone loses about 2%-4% of bone mineral density on Depo, then when they stop the injections, their BMD will recover and there is no risk," said principal investigator Dr. Zeev Harel, professor of pediatrics Brown University, Providence, R.I. "The longer they use Depo, the more shots they get, the more BMD they lose; it's somewhat more difficult to recover."

Participants included 98 healthy female adolescents between the ages of 12 and 18 who initiated depot medroxyprogesterone acetate (DMPA, Depo-Provera) intramuscular injections for contraception and provided BMD data for up to 300 weeks after cessation of DMPA. BMD was assessed by dual-energy x-ray absorptiometry at the lumbar spine, hip, and femoral neck.

During the study period, 19.4% of participants received 17 or more injections of DMPA, 15.3% received 13-16 injections, 17.3% received 9-12 injections, 24.5% received 5-8 injections, and 23.5% received 4 or fewer injections. Overall, the median total number of DMPA injections received was nine, Dr. Harel reported in a poster presentation during the annual meeting.

At the time of DMPA cessation, participants showed mean BMD declines from baseline of 2.7% at the lumbar spine, 4.1% at the hip, and 3.9% at the femoral neck.

Within 60 weeks of DMPA discontinuation, mean BMD values for the lumbar spine had returned to baseline levels. By 240 weeks, they had increased by 4.7% above baseline. Recovery occurred more slowly at the hip and femoral neck, with full recovery of mean BMD not seen until 240 weeks in the hip and 180 weeks in the femoral neck.

Postcessation gains were smaller in girls who exhibited a 5% or greater BMD loss during treatment, with mean BMD remaining below baseline at 240 weeks, also published in Contraception (2010;81:281-91).

Participants who had a 5% or greater loss of BMD had received a significantly greater number of DMPA injections (median, 13) than did those with less than 5% loss (median, 5).

The investigators noted five patient factors that affected BMD loss during DPMA treatment. Dr. Harel explained that those who had adequate calcium intake, adequate vitamin D intake, no smoking, and lower alcohol intake tended to lose less BMD during treatment. "The fifth factor, and one we have no control over, was weight," he said. "Those who were a bit more overweight tended to lose less BMD."

A 15% gain in BMD was seen in the control group. "In girls this age, over about 8-9 years, they can gain 15% in bone mineral density," said Dr. Harel. ■

VITALS

Major Finding: Within 60 weeks of DMPA discontinuation, mean BMD values for the lumbar spine had returned to baseline levels. At the hip, full recovery of mean BMD took 240 weeks and at the femoral neck, 180 weeks.

Data Source: BMD values for up to 300 weeks after cessation of DMPA in 98 healthy female adolescents who initiated the injections for contraception between the ages of 12 and 18.

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MY TAKE

Weigh the Risk-Benefit Ratio

I think Dr Harel's data are encouraging in that some of the BMD loss appears to be reversible. On the flip side, it doesn't appear that the losses were completely reversible, so one worries in a young person on Depo-Provera that she might have skeletal deficits as she reaches peak bone mass.

Having said that, I'm an adolescent medicine physician, and for some patients Depo-Provera keeps them from becoming pregnant most effectively, so I think a clinician has to very carefully weigh the risk-benefit ratio. As we know, pregnancy is a high bone turnover state, so they're breaking down their skeleton when they should be accruing it.

We don't have the long-term outcome data to say whether these girls go on to be at higher risk for osteoporosis and for fractures, but these data are sorely needed, and I think they stimulate us to want to design those long-term studies to look at the health outcomes that accompany those changes in bone density.

CATHERINE M. GORDON, M.D., *is the director of the bone health program at Children's Hospital Boston. Dr. Gordon reported no relevant financial disclosures.*