

Widespread Vit D Supplementation Questioned

BY BRUCE JANCIN

SNOWMASS, COLO. — Serious questions exist about the safety and efficacy of the popular practice of high-dose vitamin D supplementation across a broad swath of the population.

One of these concerns is that not all of the extra calcium absorption promoted by boosting vitamin D is going into bone to prevent fractures. Some of it may actually be taken up by atherosclerotic plaque, increasing the risk of cardiovascular events, Dr. Lenore M. Buckley cautioned at a symposium sponsored by the American College of Rheumatology.

This is of particular concern in patients with known coronary disease and for those at high risk, including individuals with rheumatoid arthritis, systemic lupus erythematosus, diabetes, or psoriasis, added Dr. Buckley, professor of medicine at Virginia Commonwealth University, Richmond.

Discussing findings from a recent cross-sectional study involving 340 African Americans with type 2 diabetes, Dr. Buckley said that serum 25-hydroxyvitamin D levels were positively associated with increased calcified atherosclerotic plaque in the aorta and carotid arteries (J. Clin. Endo. Metab. Jan. 8, 2010; Epub ahead of print PMID:20061416).

"The effects of supplementing vitamin D to raise the serum 25-hydroxyvitamin D level on atherosclerosis in African Americans are unknown. Prospective trials are needed," the investigators wrote.

Recently, a large prospective randomized trial assessed the effects of using calcium supplements on vascular event rates, but it did not involve African Americans. The trial involved 1,471 healthy post-

menopausal New Zealand women who were randomized to receive either supplemental calcium or placebo. By 5 years of follow-up, there were a total of 101 myocardial infarctions, strokes, and sudden deaths in 69 women in the supplemental calcium group compared to 54 such events in 42 control subjects (Br. Med. J. 2008; 336:262-6).

The numbers needed to treat (NNT) were "particularly disturbing," said Dr. Buckley. The NNT for 5 years of supplemental calcium to cause one additional MI than with placebo was 44. The NNT for one stroke was 56. And the NNT to cause one additional cardiovascular event was 29. In contrast, the NNT to prevent one symptomatic fracture was 50.

The vascular event rate was higher in women with high compliance with calcium supplementation. The event rate was also higher during months 30-60 of follow-up, consistent with an initial latent period in which silent vascular damage occurs in advance of climbing cardiovascular event rates.

The vitamin D assay has become one of the most-ordered U.S. lab tests, despite the assay's questionable reliability, its \$40-\$200 cost, and considerable unresolved debate as to what constitutes an optimal blood level. Medicare is considering changing policy such that vitamin D tests for screening purposes would not be covered, according to Dr. Buckley.

There is solid evidence that vitamin D supplementation reduces fracture risk in the elderly, especially in those with low serum levels. But that's not what's driving

the astounding recent growth in serum vitamin D screening and supplementation. The impetus for the upsurge in screening is the hope that it might protect against a broad range of chronic diseases, including cancers, dementia, autoimmune diseases, and cardiovascular disease.

The extra calcium absorption promoted by boosting vitamin D may be taken up by atherosclerotic plaque.

DR. BUCKLEY

that hope is driven mostly by epidemiologic data, which must be viewed as hypothesis-generating rather than definitive. The classic example of how misleading epidemiologic associations can be is the expectation that estrogen replacement would reduce cardiovascular risk in postmenopausal women; when the Women's Health Initiative and other prospective trials were eventually carried out, it turned out just the opposite was true, Dr. Buckley noted.

"The question we have to ask is: What does that low serum vitamin D level mean? Is it the thing that predisposes, or is it somehow a byproduct of illness?" she continued.

There is intriguing evidence to indicate the optimal level of vitamin D to promote bone health, muscle strength, immunity, and other key functions may vary by race. Data from the National Health and Nutrition Examination Survey show that very few white children ages 1-12 years are vitamin D-deficient using the classic threshold of 15 ng/mL. In contrast, about 10% of non-Hispanic black 1- to 6-year-olds are vitamin D-deficient, as are close to 30% in the 7-12 age bracket (Pediatrics Sept. 2009; e362-70; doi:10.1542/peds.2009-0051).

Many observers see this racial dispar-

ity as a public health problem reflecting unequal access to services. But there is a conundrum here: If vitamin D deficiency is rampant in black children, why do they have greater bone strength and muscle mass than whites?

"It makes one wonder whether the definition of normal levels should vary by race," according to the rheumatologist.

Support for this notion comes from studies showing that pushing serum vitamin D levels to 30 ng/mL or higher in whites reduces their parathyroid hormone levels, while pushing levels above 20 ng/mL in African Americans—young or old—does not further decrease parathyroid hormone or increase bone density.

In her own practice, Dr. Buckley generally tries to get patients into the 20- to 29-ng/mL range, while in African Americans and patients with known cardiovascular disease she aims for 15 ng/mL or slightly more, she said. She reserves expedited supplementation—50,000 IU weekly for 8 weeks—mainly for vitamin D-deficient elderly patients at high risk for fracture or fall. That's where there is supporting evidence of benefit. There is no evidence to support supplementation in young or middle-aged patients.

Like many others, Dr. Buckley eagerly awaits fresh guidance in the form of updated recommendations on vitamin D from the Institute of Medicine. That IOM report, due this spring, is expected to recommend an increase in the currently recommended supplemental 400 IU/day for 50- to 70-year-olds not getting sufficient vitamin D from the sun (see related article on p. 1). Her hope is the IOM will address the thorny issues of who should receive supplementation, and how fast it should be done.

Dr. Buckley reported having no relevant financial relationships. ■



Antiretroviral Therapy May Contribute to Bone Loss

BY SHERRY BOSCHERT

SAN FRANCISCO — People with HIV infection tend to have more risk factors for bone loss than do people without HIV, and antiretroviral medications may be adding to that risk.

The specific role of antiretroviral therapy in bone loss has been controversial: Some studies say there is no association, but others suggest that the drugs do contribute to bone loss. Results of two small but well-conducted studies recently tipped the emphasis toward concern about the differential effects of antiretrovirals on bone mineral density, Dr. Dolores Shoback said at a meeting on HIV management sponsored by the University of California, San Francisco.

One randomized, controlled trial of 71 HIV-infected patients suggested that antiretroviral regimens that contain a protease inhibitor booster have a greater negative impact on spinal bone density than do regimens without a boosted protease inhibitor, said Dr. Shoback, professor of medicine at UCSF.

At baseline, 31% of the patients were osteopenic and 3% were osteoporotic. Bone densities were retested after 48 weeks of combination HIV therapy with a non-nucleoside reverse transcriptase inhibitor (NNRTI) and nucleoside reverse transcriptase inhibitors (NRTIs), or

an NNRTI and a boosted protease inhibitor, or two NRTIs and a boosted protease inhibitor. On average, the cohort as a whole lost 4% of lumbar spine bone mineral density and 3% of hip bone density during those 48 weeks (AIDS 2009;23:817-24).

The groups treated with boosted protease inhibitors lost significantly more spinal density—4.4% when combined with an NNRTI and 5.8% when combined with NRTIs—compared with the NNRTI-plus-NRTI arm (1.5%). Changes in hip bone density did not differ significantly by treatment group.

The second study randomized 50 HIV-infected patients to treatment with lopinavir/ritonavir plus zidovudine/lamivudine (ZDV/3TC) or lopinavir/ritonavir plus nevirapine, with bone densities compared at baseline and 2 years. At the start, up to 31% were osteopenic and up to 4% were osteoporotic. The ZDV/3TC group lost 6.3% of bone mineral density in the hip and 5.1% in the spine, compared with smaller losses of 2.3% in the hip and 2.6% in the spine in the nevirapine group. Spinal density decreased mainly in the first year and then stabilized, but hip den-

sity continued to fall in the second year (AIDS 2009;23:1367-76).

The investigators speculated that ZDV/3TC increased osteoclastic activity. "I think there probably is, in fact, a signal here," Dr. Shoback said.

The evidence does not support changing antiretroviral regimens if bone mineral density is low, she added, but physicians should pay attention to nutrition (especially calcium and vitamin D), lifestyle factors, and weight-bearing exercise in patients with HIV.

Ongoing immune activation in HIV infection leads to high levels of cytokines. "There pretty much isn't a cytokine that doesn't have a negative effect on bone," she said. Also, five of six cross-sectional studies found low levels of hydroxyvitamin D in patients with HIV. Compared with the HIV-negative population, people with HIV have higher rates of smoking and alcohol use, are more likely to be treated with steroids, and are more likely to have periods of immobilization and illness, bouts of weight loss, hypogonadism (in men), and amenorrhea (in women).

Dr. Shoback has been a speaker for Novartis. ■



HIV patients on antiretroviral regimens with a protease inhibitor booster have shown greater bone loss.

DR. SHOBACK