Bone Loss in Teens on DMPA Tied to Vitamin D

BY ROBERT FINN

LAS VEGAS — Abnormally low levels of vitamin D were seen in a subset of 15 adolescent girls who had substantial losses in bone mineral density while using depot medroxyprogesterone acetate for contraception, according to preliminary results from a prospective study presented at the annual meeting of the North American Society for Pediatric and Adolescent Gynecology.

VITALS

Major Finding: In a substudy of 15 adolescent girls with significant bone loss while using depot medroxyprogesterone acetate, only 1 participant had a "sufficient" serum vitamin D level of greater than 30 ng/mL.

Data Source: Subset of a prospective study of 181 adolescent girls on depot medroxyprogesterone acetate.

Disclosures: The study was sponsored by Pfizer/Pharmacia, and one of the investigators was employed by that company. Dr. Harel disclosed financial relationships with Merck, Teva/Duramed, Ortho-McNeil, GlaxoSmithKline, Novartis, and Warner Chilcott.

The girls were among 181 adolescents using depot medroxyprogesterone acetate (Depo-Provera, Pfizer) in a prospective study. Bone mineral density (BMD) losses of 5% or more were seen at the lumbar spine in 25% and at the hip in 50% of the study participants.

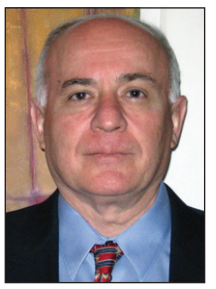
The relative estrogen deficiency associated with depot medroxyprogesterone acetate (DMPA) did not correlate with the magnitude of BMD loss, according to Dr. Zeev Harel of Brown University in Providence, R.I.

Moreover, serum estradiol remained above 40-50 pg/mL in almost all participants, Dr. Harel said. This level is considered to be sufficient to conserve bone in elderly women.

Dr. Harel and his colleagues examined a subset of 15 young women who lost at least 5% of BMD from baseline. Their average age was 17 years, and they were an average of 61 months postmenarche. Their BMIs were within the normal range, and none was obese. Their ethnicity was diverse and they resided in various U.S. locations.

Investigators noted BMD losses in the majority of the 15 girls after two or three DMPA injections, but some participants did not exhibit BMD losses until after their 10th or 13th injection.

Serum 25-hydroxyvitamin D (25[OH]D) levels were available for 14 of the 15 girls, and all but 1 had low levels of vitamin D. Levels above 30 ng/mL are considered sufficient, levels between 20-30 ng/mL are referred to as "insufficient," and levels below 20 ng/mL are referred to as "deficient." Seven of the 14 participants (50%) were vitamin D insufficient, 6 (43%) were vitamin D deficient, and 1 (7%) had normal levels of vitamin D. The mean serum 25(OH)D level among the participants was about 25 ng/mL, in the insufficient range.



Mean levels of parathyroid hormone, on the other hand, were in the normal range.

In an interview, Dr. Harel expressed surprise at these results. "I was expecting probably less than 30% [of the participants would have low levels of vitamin D]," he said

"We were surprised specifically because when we drew the blood we did it at the end of the summer. Typically we absorb vitamin D from the sun. Also, most of the patients were Caucasian. We know that vitamin D deficiency is common in African Americans and Hispanics. Also, they were not extremely obese. We know we can find vitamin D deficiency in obesity. And we also had representatives from states that were really sunny, California for example."

Dr. Harel emphasized at the meeting that the results were preliminary. Additional studies would require a comparison group of young women on depot medroxyprogesterone acetate who did not experience declines in BMD. And he said that it would be important to study whether vitamin D supplementation would reverse the decline in BMD.

'We were surprised ... because when we drew the blood we did it at the end of the summer.'

DR. HAREL

Still, Dr. Harel found results sufficiently worrisome to recommend close monitoring of young women on depot medroxyprogesterone acetate. "We know in the adult elderly population that many are aware of their vitamin D status. In adolescents still we are in the beginning," he said. He recommended that total 25(OH)D status be measured in all adolescent girls using depot medroxyprogesterone acetate. "And if it's low—deficient or insufficient—treat it accordingly.

"The current recommendation if we have a patient with vitamin D deficiency is to take 50,000 IU once a week for 8 weeks and then repeat the total 25(OH)D. Those who have insufficient vitamin D, we typically treat with 800 IU of vitamin D a day and we do it for 3 months, and then again we repeat the total 25(OH)D," Dr. Harel said at the meeting. ■

Vitamin B Therapy Worsens Renal Function, Vascular Events

BY MARY ANN MOON

A study testing the hypothesis that vitamin B therapy would slow the progression of diabetic nephropathy and prevent vascular events instead showed just the opposite: Use of high-dose B vitamins worsened renal function and raised the rates of MI and stroke, according to Dr. Andrew A. House of the University of Western Ontario, London, and his associates.

"Our trial is the first study to our knowledge to show significant detrimental effects from pharmacological doses of B vitamins," they said.

Vitamin B therapy lowers plasma concentrations of homocysteine and improves endothelial function, but most clinical trials in which high-dose B vitamins have been used to decrease homocysteine have failed to demonstrate improved cardiovascular outcomes, according to the researchers (JAMA 2010;303:1603-9).

"Given the recent large-scale clinical trials showing no treatment benefit, and our trial demonstrating harm, it would be prudent to discourage the use of high-dose B vitamins as a homocysteine-lowering strategy outside the framework of properly conducted clinical research," Dr. House and his colleagues concluded.

The investigators tested their hypothesis that vitamin B therapy would improve nephropathy and vascular events in a study of 238 adults with type 1 or 2 diabetes and stages 1-3 chronic kidney disease who were treated at five university medical centers in Canada.

'Given ... our trial demonstrating harm, it would be prudent to discourage the use of high-dose B vitamins as a homocysteine-lowering strategy.'

The participants were randomly assigned in equal numbers to receive either a daily tablet containing folic acid (2.5 mg/day), vitamin B_6 (25 mg/day), and vitamin B_{12} (1 mg/day) or a matching placebo. They were followed every 6 months for up to 3 years (mean follow-up, 32 months).

As expected, plasma homocysteine levels decreased in the group taking vitamin B therapy but increased in those taking placebo, resulting in a significant mean difference of 4.8 micromol/L between the two groups.

Nevertheless, compared with patients assigned to placebo, those assigned to the B vitamin group had a much greater decrease in renal function, as assessed by one direct and two indirect methods: radionuclide glomerular filtration rate (GFR), estimated GFR using creatinine clearance, and estimated GFR using the Modification of Diet in Renal Disease (MDRD) formula.

"Over 36 months, the GFR decreased by a mean of 16.5 mL/min/1.73 m^2 in the B-vitamin group, compared with 10.7 mL/min/1.73 m^2 in the placebo group, a significant mean difference of –5.8," Dr. House and his associates wrote.

There were no differences between the two groups in measures of proteinuria or in need for dialysis.

Participants who received vitamin B therapy also had approximately twice as many cardiovascular and cerebrovascular events as those who received placebo. The 3-year risk of a composite outcome that included MI, stroke, revascularization, and all-cause mortality was 23.5% in the vitamin B group and 14.4% in the placebo group.

The two groups did not differ in rates of all-cause mortality, amputation, or cognitive decline.

The rates of adverse events (88%-90%) and severe adverse events (32%-33%) were not significantly different between the two groups. The rate of serious adverse events was slightly higher in the placebo group (40%) than in the active treatment group (34%).

The study findings suggest that vitamin B therapy is associated with both renal and vascular toxicity. Possible explanations are that folic acid may promote cell proliferation through its role in thymidine synthesis; that folic acid and B_{12} might alter the methylation potential in vascular cells; or that all the components of vitamin B therapy might increase the methylation of l-arginine to asymmetric dimethylarginine, a nitric oxide synthase inhibitor.

It also is possible that the decrease in homocysteine is actually protective, but that this benefit may be offset by the treatment's toxicity, Dr. House and his associates said.

The study was supported by the Canadian Institutes of Health Research and the Kidney Foundation of Canada. Pan American Laboratories provided the B vitamins and placebos. Dr. House and an associate reported having a patent pending on the use of mesna to reduce homocysteine levels in patients on dialysis. The same associate reported receiving fees from Pan American Laboratories and Medice Arzneimittel Pütter GmbH. ■