Physiologic Estrogen Boosts BMD in Anorexia

BY AMY ROTHMAN SCHONFELD

FROM THE ANNUAL MEETING OF THE ENDOCRINE SOCIETY

BOSTON – Significant increases in bone mineral density at the spine and hip were seen in adolescent girls with anorexia nervosa treated with physiological doses of estrogen, as compared with placebo, according to Dr. Madhusmita Misra, who presented the findings at the meeting.

"We know that low bone mineral density is common in adolescent girls with anorexia nervosa. On dual-energy x-ray absorptiometry (DXA), about 50% have low *z* scores at one or more sites and they also have low bone accrual rates. This is a special concern during adolescence, when peak bone mass accrual normally occurs," said Dr. Misra, a pediatrician at Harvard Medical School and Massachusetts General Hospital in Boston.

'This is a strategy to optimize bone accrual in girls with anorexia nervosa, even if they are not recovering.'

DR. MISRA

While previous studies have shown that giving oral estrogen combined with progesterone as birth control pills is not effective at increasing bone density in these girls, the effect of giving estrogen in a more natural or physiologic form to mimic puberty or as a transdermal patch had not been studied before.

VITALS

Major Finding: Physiologic doses of estrogen significantly increased bone mineral density *z* scores in the lumbar spine and hip in adolescent girls with anorexia nervosa.

Data Source: A prospective trial of 110 girls with anorexia nervosa randomized to receive estrogen replacement or placebo, and 40 healthy controls who were followed for 18 months.

Disclosures: Dr. Misra received support from Genentech.

In a prospective, randomized study, 110 girls with anorexia nervosa and 40 normal-weight girls of similar pubertal stage and bone age between the ages of 12 and 19 years were enrolled. The girls with anorexia nervosa were randomized to receive either placebo or estrogen, but which type of estrogen they received depended upon their bone maturity based on wrist and hand x-rays.

In order to avoid adversely affecting growth with estrogen, those with immature bone age (n = 14) received low-dose oral ethinyl estradiol in gradually increasing doses (3.75 mcg daily for 0-6 months, 7.5 mcg daily for 6-12 months, and 11.25 mcg daily for 12-18 months) while those with mature bone age (n = 96) received transdermal estradiol at full replacement doses (100 mcg 17-beta estradiol). All received calcium and vitamin D supplementation and were followed for 18 months (J. Bone Miner. Res. 2011 June 22 [doi.10.1002/jbmr.447]).

The results showed that after 18 months, spine and hip bone mineral density *z* scores increased significantly in girls with anorexia nervosa who received estrogen replacement, compared with those who received placebo, even after controlling for baseline age and weight.

Changes in lumbar bone mineral density were significantly lower at 6, 12, and 18 months in anorexic girls who did not receive estrogen, compared with either anorexic girls who received estrogen or healthy controls.

No significant differences were seen in these measures between anorexic girls who received estrogen and healthy controls. Similar trends were seen for hip bone mineral density, with significant differences at all time points between non–estrogen-treated anorexic girls and healthy controls; differences between treated and untreated anorexic girls were significant only at 18 months.

The two anorexic groups did not differ in body mass index, fat mass, or lean mass after estrogen treatment, indicating that estrogen replacement does not cause weight gain or changes in body composition.

"This is very encouraging and exciting data," said Dr. Misra.

"I would strongly emphasize that the first step in treating anorexia nervosa has to be to encourage weight gain and menses resumption. As we know, there may be many girls who are recalcitrant about formal treatment, and the adolescent years are a difficult time to accrue bone mass. This is a strategy to optimize bone accrual in girls with anorexia nervosa, even if they are not recovering otherwise."

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She added that it was important to note that although estrogen replacement improves bone density, it often falls short of complete restoration of bone density to normal levels. ■

Link Between Chronic PPI Use, Hip Fractures Confirmed

BY CAROLINE HELWICK

FROM THE ANNUAL DIGESTIVE DISEASE WEEK

CHICAGO – Regular use of proton pump inhibitors is associated with an elevated risk of hip fractures, even after adjusting for important lifestyle risk factors, according to the findings of a prospective evaluation from the Nurses' Health Study.

'We found that longer duration of use was associated with increased risk, and the strongest risk was confined to individuals with a history of smoking.'

The association was most striking for women with a history of smoking, observed Dr. Hamed Khalili of Massachusetts General Hospital, Boston.

The Food and Drug Association recently issued an advisory regarding a potential link between PPIs and fractures. While acid-suppressing medications have been hypothesized to increase the risk of osteoporotic fractures, studies examining this association have been inconsistent. These analyses have mostly been based on retrospective studies of small populations that have not controlled for important dietary and lifestyle confounders, and they have ascertained PPI use only at a single time point, Dr. Khalili said.

The current study aimed to be more definitive by prospectively examining the relationship between chronic PPI use and incident hip fracture among 79,899 postmenopausal women enrolled in the Nurses' Health Study, he said.

"We found that longer duration of use was associated with increased risk, and the strongest risk was confined to individuals with a history of smoking. … Our findings support the recent decision of the FDA to revise labeling of PPIs to incorporate concerns about a possible increase in the risk of fractures," he said at the meeting.

In 1982, participants in the Nurses' Health Study were first asked to report all previous fractures and were queried biennially for new fractures. Among the nearly 80,000 subjects, with 565,786 person-years of follow-up, there were 893 incident hip fractures over 8 years. PPI use was reported by 7% of participants in 2000 and by 19% of participants in 2008.

VITALS

Major Finding: Regular use of PPIs posed fracture risks of 35%-45% when adjusted for age, calcium intake, and body mass index. The fully adjusted hazard ratio was 1.37.

Data Source: A prospective examination of the relationship between chronic PPI use and incident hip fracture among 79,899 postmenopausal women enrolled in the Nurses' Health Study.

Disclosures: Dr. Khalili reported having no conflicts of interest.

Regular use of PPIs posed fracture risks of 35%-45% when adjusted for age, calcium intake, and body mass index. The fully adjusted hazard ratio was 1.37, Dr. Khalili reported.

Current smoking status stood out as a significant effect modifier. Women who were current or past smokers and who regularly took a PPI had a 51% increased risk for fracture. In contrast, women who never smoked had only a 6% increased risk, "almost equal to women who never used PPIs," he noted.

Longer duration of use was significantly associated with greater risk. Compared with never-users, risk in the multivariate analysis was 36% after 2 years of use, 42% after 4 years and 54% when PPIs were used for 6 years or longer, he said.

The investigators adjusted for multiple other risk factors, including physical activity; alcohol intake; total daily calcium and vitamin D intake; history of osteoporosis; and use of hormone replacement therapy, bisphosphonates, and thiazides. "This did not materially alter this association," he noted.

When PPIs were discontinued, the risks declined. Two or more years after discontinuation, the risk of hip fracture was just 9%-10%, he noted.

"The strengths of our study are that it offers detailed, prospectively collected and validated information on PPI use and other risk factors. We had a high response rate, and the participants are educated health professionals," he said. "But the study lacks information about PPI use prior to 2000, and it lacks specific information about brand and dose of PPI. It's not clear whether this is generalizable to other populations."

The study, however, is in line with other reports of an association, and adds weight to the recommendation that clinicians carefully monitor the necessity of postmenopausal women to continue taking PPIs over the long-term, especially those who smoke.

Response from the audience was robust, with one attendee noting, "This is truly excellent work," and another calling the study "impressive." ■