ASK THE EXPERT

Osteoporosis in Pediatric Rheumatic Disease

Chronic inflammatory diseases in children and adolescents can have a detrimental effect on bone mass, compromising bone growth and development during prime bone-building years. Therefore, the increased risk of osteoporosis and fragility fractures among pediatric patients with conditions such as juvenile arthritis, systemic lupus erythematosus (SLE), and dermatomyositis must be addressed early to prevent long-term pain and disability, according to pediatric rheumatologist Philip J. Hashkes of Shaare Zedek Medical Center in Jerusalem.

Guidelines for osteoporosis treatment in adults are widely accepted, but management in the pediatric population is not as well defined because of the relative lack of substantive data on children and adolescents with osteoporosis, he said.

We asked Dr. Hashkes to discuss the underlying mechanisms for osteoporosis in juvenile patients with rheumatic disease, as well as optimal management strategies.

Clinical Endocrinology News: Glucocorticoid use is widely recognized as a risk factor for osteoporosis in children with rheumatic diseases, but multiple studies have revealed that the increased risk of compromised bone development can precede the onset of steroid therapy in these patients. What are the presumed mechanisms for this increased risk?

Dr. Hashkes: Besides steroid therapy, several other mechanisms may promote osteoporosis, like the disease process itself—specifically cytokines that promote osteoclast activation, for example interleukin-6. Inactivity or immobilization, especially lack of weight bearing as a result of arthritis or myositis, is a major contributor to osteoporosis. Lack of intake of foods containing calcium and vitamin D due to anorexia, related to inflammation or temporomandibular joint arthritis, is another contributor. Patients with inflammatory diseases that affect absorption (dermatomyositis) or renal function (SLE) may have impaired bone metabolism. Another treatment-related factor with the potential to cause vitamin D deficiency is sun protection or a lack of sun exposure, which is recommended for patients with SLE and dermatomyositis.

CEN: What are some of the challenges that clinicians face in diagnosing osteoporosis in this population?

Dr. Hashkes: The first issue is realizing that osteoporosis is not only a disease of older people. This disease also can occur in certain childhood conditions. The gold standard for diagnosing osteoporosis is dual-emission x-ray absorptiometry (DXA). However, the problem with pediatric DXA studies is the overdiagnosis of osteoporosis due to misinterpretation of data based on adult references. Bone density varies greatly with age. This is the reason the densitometry *z* scores based on pediatric reference curves are used in the pediatric population and not the T score usually used in adults. Also the definition of osteoporosis is different in children than in adults.

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CEN: Is there a routine osteoporosis screening protocol for children who are newly diagnosed with any of these rheumatic diseases?

Dr. Hashkes: In general, children who need steroid therapy for at least 3 months should undergo baseline DXA testing, as well as periodic DXA scans, depending on the dose of steroids and other factors. There are no evidence-based guidelines regarding whether children with rheumatic diseases not treated with steroids need to undergo routine DXA screening. The issue of vitamin D screening has also not been resolved.

CEN: What are the recommended prevention interventions for children diagnosed with juvenile arthritis or another rheumatic condition without evidence of osteoporosis?

Dr. Hashkes: Ensure that these children have an adequate intake of calcium (500 mg/day for 1- to 3-year-olds, 800 mg/day for 4- to 8-year-olds, and 1,300 mg/day for 9- to 18-year-olds) and vitamin D (at least 400 U/day). The composition of the diet may be important for calcium utilization, with improved absorption in patients consuming a Mediterranean-type diet.

CEN: What are the current treatment options for osteoporosis in this population, and what are some of the important considerations for initiating and managing treatment over time?

Dr. Hashkes: In addition to being used for the dietary issues I mentioned, bisphosphonates can be used in children who have suffered fractures or have extreme osteopenia on a DXA scan. However, for primary prevention, the use of bisphosphonates in children receiving corticosteroids is still not recommended. The safety profile of bisphosphonates in children has been good with minimal effects on growth and on development of normal bone. Additional caution must be given to children needing dental work, including orthodontics, regarding the potential development of jaw osteonecrosis—although this has not yet been reported in children—and to adolescent females with the potential for childbearing. Bisphosphonates have an extremely long bone half-life, and the effect on the fetus is still not clear. There may be a difference between various agents in the bone half-life that may impact the decision on which agent to use.

CEN: Often children with rheumatoid disease are treated by adult versus pediatric specialists. In terms of assessing and managing osteoporosis in children versus adults, what advice can you provide?

Dr. Hashkes: The main issue is awareness. Osteoporosis can occur in children with chronic inflammatory conditions whether they are or are not treated with steroids. Clinicians need to be aware of correct pediatric interpretations of DXA scans, and to ensure the machine has pediatric software. They need to be aware of the increased dietary requirements of calcium and vitamin D in growing children. Recombinant human parathyroid hormone should not be used in children because of potential safety issues, including the potential for the development of bone tumors.

—Diana Mahoney

Dr. Hashkes *is the head of the pediatric rheumatology unit at Shaare Zedek Medical Center in Jerusalem. He reported no conflicts of interest.*

Oral Bisphosphonates Not Linked to Esophageal, Gastric Ca

BY MARY ANN MOON

From JAMA

The use of oral bisphosphonates was not associated with esophageal or gastric cancer in a large cohort study in the United Kingdom, according to a large U.K. database analysis.

Oral bisphosphonates cause serious esophagitis in some users. Reflux esophagitis is a known risk factor for esophageal cancer, but it is not known whether bisphosphonates-associated esophagitis also predisposes patients to develop gastric cancer, said Chris R. Cardwell, Ph.D., of Queen's University Belfast (Ireland), and his associates.

"The U.S. Food and Drug Administration recently reported 23 cases of esophageal cancer (between 1995 and 2008) in patients using the bisphosphonate alendronate and a further 31 cases in patients using bisphosphonates in Europe and Japan, possibly indicating risk of malignancy," the investigators noted.

They searched for a possible link between the drugs and esophageal or gastric cancer using the General Practice Research Database (GPRD), "the world's largest computerized database of anonymized longitudinal patient records," which includes 500 general practices and covers about 6% of the population in the United Kingdom.

The investigators reviewed the records of 41,826 patients aged 40 years and older who used bisphosphonates and the same number of control patients matched for age, sex, and medical practice.

During a mean follow-up of 4.5 years, 287 of these patients developed esophageal or gastric cancer.

The risk of these cancers was no higher in patients who took larger daily doses of bisphosphonates or in those who had a longer duration of bisphosphonate use.

There were no significant differences between cases and controls in risk for esophageal cancer, gastric cancer, or both cancers combined.

This result did not change when the data were adjusted to account for possible confounders of gastric cancer risk, such as smoking, alcohol use, and use of drugs including NSAIDs, proton pump inhibitors, and H_2 receptor antagonists.

Moreover, the risk of these cancers was no higher in patients who took larger daily doses of bisphosphonates or in those who had a longer duration of bisphosphonate use, the investigators said (JAMA 2010;304:657-63).

In addition, the risk of gastric cancer was not significantly different between men and women exposed to bisphosphonates, and it did not differ across several different bisphosphonate medications.

There also was no association between cancer risk and bisphosphonate use in the subgroup of patients who had a history of gastroesophageal reflux disease.

Previous studies of this issue were limited by very small numbers of cases and short follow-up, lack of adjustment for potential confounders, and lack of differentiation between bisphosphonates by type, dosage, or duration of use, Dr. Cardwell and his associates noted.

"In conclusion … we found no evidence for a substantially increased risk of esophageal (or gastric) cancer in persons using oral bisphosphonates.

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Dr. Cardwell reported no financial conflicts of interest. ■