

## Clinical Update

### New evidence of a link between inhaled corticosteroid use and osteoporosis

**Wong CA, Walsh LJ, Smith CJ, Wisniewski AF, Lewis SA, Hubbard R, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* 2000;355(9213):1399-403.**

#### Background

Although systemic corticosteroid therapy is a well-recognized risk factor for osteoporosis, the effect of chronic inhaled corticosteroid (ICS) use on bone mineral density is uncertain.<sup>1</sup> The relationship between ICS and bone mineral density has been difficult to assess because of potential confounding variables such as age, use of oral corticosteroids and lower activity levels in patients with asthma.

#### Question

Is inhaled corticosteroid use associated with decreased bone mineral density in patients with asthma?

#### Design

This cross-sectional study recruited patients with asthma between 20 and 40 years of age from primary care practices and from an asthma research registry in Nottingham, England. Patients had taken an inhaled corticosteroid regularly for at least 6 months; exclusion criteria included the use of oral and parenteral steroids on more than 2 occasions or within 6 months of the study. The patients completed an extensive health questionnaire, which included a detailed medical history, risk factors for osteoporosis and questions about occupation, lifestyle, diet and medication use. Reported use of corticosteroids in all formulations (i.e., inhaled, oral, nasal

and dermal) was recorded and validated by an independent researcher using available health records. This information was used to calculate a cumulative dose of ICS for each patient. Bone mineral density of the femoral neck and the lumbar spine of each patient was measured using dual-energy x-ray absorptiometry. Multiple linear regression analysis using a priori confounders of age and sex assessed the relationship between cumulative dose of ICS and bone mineral density. Other variables associated with bone mineral density were then evaluated in the regression model.

#### Results

Of the 196 subjects who participated in the study, 119 (61%) were women, and all but 20 were recruited from primary care practices. The median duration of corticosteroid treatment was 6 years, and the mean forced expiratory volume (1 s) was 93% predicted. Beclomethasone was the ICS for 80% of the subjects, 9% of whom had started taking inhaled corticosteroids before the age of 15; almost half (45%) had never taken a course of oral corticosteroids.

The median cumulative dose of ICS was 876 mg (roughly 500 mg per day for 5 years). A doubling of the cumulative dose of ICS was associated with a decrease in bone mineral density of 0.023 g/cm<sup>3</sup> (95% confidence interval [CI] 0.005–0.041) at the lumbar spine and a decrease of 0.020 g/cm<sup>3</sup> (95% CI 0.002–0.038) at the femoral neck compared with age-matched reference data. Similar results were obtained for the duration of ICS therapy. Adjustments for factors such as smoking, calcium intake and exercise did not affect the results significantly.

#### Commentary

This study demonstrates an inverse relationship between bone mineral density and the cumulative dose and duration of ICS therapy in patients with asthma. The investigators minimized potential confounding variables by using young patients with mild asthma and by excluding patients who had received more than 2 courses of oral corticosteroids. Validating subjects' reported steroid use with health records helped to minimize recall bias.

#### Practice implications

There is good evidence that the use of low-dose inhaled corticosteroids has improved asthma treatment over the past decade.<sup>2</sup> This study draws attention to the potential risk of osteoporosis in patients who require long-term ICS therapy. To minimize this risk, physicians should ensure that their patients are on the lowest effective dose of ICS and encourage them to undertake simple measures such as regular exercise and an adequate calcium intake to optimize bone density. Although none of the subjects in this study showed evidence of vertebral fractures, longitudinal studies are required to evaluate whether patients treated with ICS are at higher risk for fractures. — *Kathryn A. Myers*

The Clinical Update section is edited by Dr. Donald Farquhar, head of the Division of Internal Medicine, Queen's University, Kingston, Ont. The updates are written by members of the division.

#### References

1. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. *Arch Intern Med* 1999;159:941-55.
2. Suissa S, Ernst P, Benayoun S, Baltzam M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343(5):332-6.