



Q/ Do inhaled steroids reduce bone mineral density and increase fracture risk?

EVIDENCE-BASED ANSWER

A | no, except perhaps at high doses. Inhaled corticosteroids (ICS) at low to medium doses (<1500 mcg beclomethasone hydrofluoroalkane per day) for asthma and chronic obstructive pulmonary disease (COPD) don't increase the risk of significant bone loss or fracture at 2 to 3 years follow-up (strength of recommendation

[SOR: **A**, systematic reviews and randomized controlled trials [RCTs]). Higher doses, however, may raise the risk of nontraumatic fracture over 1 to 4 years of follow-up (SOR: **B**, case control studies).

Experts recommend using the lowest effective dose to mitigate potential bone risks (SOR: **C**, expert consensus).

Evidence summary

A 2008 Cochrane review examined 7 RCTs comparing ICS with placebo in 1989 patients 30 to 52 years of age with mild asthma or COPD. The reviewers found no evidence of increased bone turnover, decreased bone mineral density, or increased vertebral fracture in the ICS group compared with the placebo group at 2 to 3 years' follow-up (odds ratio [OR] for fracture=1.87; 95% confidence interval [CI], 0.5-7.0).

Steroid doses ranged from 200 to 4000 mcg beclomethasone equivalent ICS per day.¹ A 100-mcg beclomethasone equivalent ICS dose is 50 mcg fluticasone, 80 mcg budesonide, or 200 mcg triamcinolone.²

A 2008 meta-analysis of 11 RCTs that examined a number of adverse effects of ICS in adult patients with COPD found 3 studies (8131 patients) that reported no significant increase in fracture risk at 36 months in the ICS group compared with the placebo group (OR=1.09; 95% CI, 0.89-1.33). Steroid doses ranged from 1000 to 2000 mcg beclomethasone equivalent ICS per day.³

Some studies suggest an association between dose and risk

A 2008 meta-analysis that included patients

with COPD or asthma, average age 43 to 81 years, showed no difference in fracture risk overall at 1 to 4 years' follow-up (OR=1.02; 95% CI, 0.96-1.08). This analysis examined 4 RCTs, 6 case-control studies, and 3 cohort studies.⁴

A subgroup analysis of patients taking higher-dose ICS (>1500 mcg beclomethasone equivalent ICS per day) that pooled data from case-control and cohort studies suggested an increased risk of fracture (OR=1.30; 95% CI, 1.07-1.58).⁴

Investigators identified a possible dose-dependent relationship in another meta-analysis of 5 case-control studies (43,783 cases, 259,936 controls).⁵ The meta-analysis included 4 of the studies examined in the previously discussed meta-analysis.⁴

The investigators found a relative risk of 1.12 (95% CI, 1.0-1.26) for nonvertebral fracture for each 1000-mcg increase in beclomethasone equivalent ICS dose per day.⁵ Longer follow-up time wasn't associated with greater fracture risk.

But the relationship isn't clear

Although some non-RCT studies discussed here show that higher doses of steroids may lead to increased fracture risk, the strength of this association isn't clear. The authors of

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the Cochrane review and the meta-analyses point out that a significant number of confounding factors can put asthma and COPD patients at increased risk for fracture. They include age, smoking status, inactivity, and severity of underlying lung disease. The fact that different authors controlled differently for these factors introduced heterogeneity into the meta-analyses described here.^{1,3-5}

Recommendations

Guidelines for the Diagnosis and Manage-

ment of Asthma from the National Heart, Lung, and Blood Institute state that “most benefit is achieved with relatively low doses of ICS, whereas the risk of adverse effects increases with dose. ... ICS use may be associated with a dose-dependent reduction in bone mineral content, although low or medium doses appear to have no major adverse effect. Elderly patients may be more at risk due to preexisting osteoporosis, changes in estrogen levels that affect calcium utilization, and a sedentary lifestyle.”⁶ **JFP**

References

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