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Commentary

Bisphosphonates for Prevention of Bone Loss in Glucocorticoid-Treated Young People

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Bone loss and the resulting fractures are among the most concerning side-effects from the use of glucocorticoid drugs in adults. Glucocorticoids act at many levels on bone, but their principal effect is to reduce bone formation through direct effects on osteoblasts and osteocytes. Most therapies developed for postmenopausal osteoporosis have also undergone trials in the treatment and prevention of glucocorticoid-induced osteoporosis. These studies have demonstrated positive effects on bone density, and some have also found evidence of prevention of vertebral fractures, even though this was not the primary endpoint of those studies [1].

The management of glucocorticoid-induced osteoporosis in children and adolescents has been an area of uncertainty for several reasons: it is not clear how frequently steroid-induced bone loss results in fractures in these groups; the difficulties of doing trials in younger people have prevented the systematic examination of the effects of osteoporosis drugs in this context; there has been concern regarding the effects of bone-active drugs on skeletal growth, and on the safety of subsequent pregnancy in girls.

Cross-sectional studies indicate that spine bone density is reduced by about 20% in children with juvenile idiopathic arthritis treated with glucocorticoids, compared with patients with the same diagnosis not receiving steroids [2], but a meta-analysis of prospective studies did not demonstrate a reduction in spine Z-scores [2]. Studies of fracture incidence or prevalence generally involve small numbers of subjects or are based on patients with mostly short-term or intermittent steroid use. These reports find that from 2% to 45% of **pediatric** patients have fractures during steroid treatment [2]. Frequent courses and higher doses of steroids are associated with higher fracture prevalence [3]. A prospective 12-month study after glucocorticoid initiation in children with rheumatic diseases found a 6% incidence of vertebral fracture, most fractures occurring in those with spine Z-scores <— 2 [4]. In 186 **pediatric** patients with acute lymphoblastic leukemia, 33% developed vertebral fractures and 23% non-vertebral fractures in the 6 years following glucocorticoid initiation, with 71% of these fractures in the first 2 years. Baseline vertebral fracture, cumulative glucocorticoid dose, and baseline spine bone density were predictive of fracture [5].

The study of Rooney et al. [6] in this issue of *EClinicalMedicine* is an important step towards providing therapeutic interventions to prevent steroid-induced bone loss in **pediatric** practice. In a comparison of weekly risedronate with daily alfacalcidol or placebo in 217 participants aged 4–18 years with chronic inflammatory rheumatic disease, risedronate is shown to have positive effects on spinal bone density, whereas alfacalcidol is no different from placebo. All participants received daily calcium and vitamin D. The positive effects of risedronate on bone density, when expressed as percent of baseline values, represent an advantage of about 5% in comparison with placebo. This is comparable to the effects seen over a similar 12-month period in adult studies [7]. There was only one definite vertebral fracture in the study, and 11 non-vertebral fractures, without significant between-group differences in fracture frequency. Thus, it seems that bisphosphonates have similar effects on bone density in young people as in adults, but active vitamin D metabolites are much less effective, as has been found in more recent adult studies [8]. Both agents were well tolerated.

The Rooney study establishes that we can prevent bone loss in young people treated with steroids, so the next key question is when this should be used. While the anti-fracture efficacy of bisphosphonates is not established in steroid-treated children, fracture prevention is the main reason for intervening. Steroid-induced bone loss is reversible [9], so if a patient's current bone density and the planned duration of steroid treatment suggest a low fracture risk, then observation alone may suffice. On the other hand, in patients with prevalent fracture, markedly reduced bone density, or the expectation of long-term, high-dose glucocorticoid use, concurrent administration of a bisphosphonate to protect the skeleton is very sensible.

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Thus, the present study indicates that risedronate, and probably other potent bisphosphonates, can provide bone preservation in children and young people receiving therapeutic doses of glucocorticoid drugs, whereas alfacalcidol is without benefit. The targeted use of bisphosphonates in children and young people judged to be at significant fracture risk is appropriate. However, whether preventing loss of bone density will reduce fracture incidence remains to be established.

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