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Is long-term glucocorticoid therapy associated with a high prevalence of asymptomatic vertebral fractures?

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Abstract

BACKGROUND—Chronic administration of glucocorticoids is associated with bone loss and increased fracture risk, particularly in the trabecular bone of the vertebrae.

OBJECTIVE—To assess the prevalence of asymptomatic vertebral fractures in postmenopausal women undergoing long-term glucocorticoid therapy.

DESIGN AND INTERVENTION—This was a multicenter, cross-sectional outpatient study of postmenopausal women. Inclusion criteria included age >45 years, glucocorticoid therapy for ≥ 6 months with a cumulative dose ≥ 1.35 g of a prednisone equivalent, and diagnosis of rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, other vasculitides or connective tissue diseases, asthma, or chronic obstructive pulmonary disease. Patients with back pain, previous vertebral fracture, Paget's disease, or using antiosteoporotic medication were excluded; however, calcium and vitamin D supplements were permitted. Participants underwent a medical interview that assessed socio-demographic factors, details of glucocorticoid therapy, and risk factors for osteoporosis. Health-related quality of life was evaluated with the European Foundation for Osteoporosis questionnaire. A back-function questionnaire rated the participants' ability to perform activities of daily living. Vertebral fractures were identified from lateral and antero-posterior thoracolumbar radiographs. Hip and lumbar spine BMD were assessed by dual energy X-ray absorptiometry and quantitative ultrasound.

OUTCOME MEASURE—The primary outcome measure was the prevalence of asymptomatic vertebral fractures.

RESULTS—The study enrolled a total of 551 women (median age 65.2 years). Rheumatoid arthritis was the most common reason for glucocorticoid therapy (53.2%). One or more asymptomatic vertebral fractures were present in 37.02% of participants, whereas 14.42% had two or more fractures. A bimodal distribution of these fractures was observed, with peaks at the T7 and T11 thoracic vertebrae. The prevalence of asymptomatic vertebral fractures increased with age; 47.98% of participants ≥ 70 years of age presented with at least one fracture ($P = 0.006$). There was a strong association between polymyalgia rheumatica and fracture prevalence; 51.09% of affected patients had one or more fracture ($P = 0.012$). When the data were adjusted for age, cumulative glucocorticoid dose, therapy duration, and fracture history, however, this association became weaker (43.20%), and was similar to the fracture prevalence of 43.36% observed in patients with other vasculitides or connective-tissue diseases. There was no correlation between fracture prevalence and cumulative glucocorticoid dose or therapy duration. Additionally, lumbar spine and hip BMD, calcaneal bone

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Competing interests

The author declared he has no competing interests.

stiffness, and health-related quality of life were not associated with the number or severity of vertebral fractures. Time since menopause and history of nonvertebral fractures both showed a significant association with asymptomatic vertebral fracture ($P < 0.001$ and $P = 0.002$, respectively). Back function score showed a modest association with the number of asymptomatic vertebral fractures.

CONCLUSION—A high prevalence of asymptomatic vertebral fractures was observed in postmenopausal women undergoing long-term glucocorticoid therapy, which suggests a need for careful evaluation of this patient subgroup.

Keywords

glucocorticoid; osteoporosis; postmenopausal; vertebral fracture

Bone loss in glucocorticoid-induced osteoporosis is biphasic, with a rapid reduction in BMD of 6–12% within the first year, followed by a slower annual loss of ~3%; however, there is more to consider than just reduced BMD.¹ Bone quality is also an issue. Importantly, the relative risk of fracture increases rapidly and escalates by as much as 75% within the first 3 months after initiation of steroid therapy. This effect is offset shortly after discontinuation of therapy, which suggests that glucocorticoids do more than just decrease bone mass.² Consistent with these data, glucocorticoid-treated patients with vertebral fractures are about 10 years younger, have higher BMD, but suffer twice the risk of fracture than patients with vertebral fractures caused by postmenopausal osteoporosis.²

The explanation for this mismatch between bone quantity and quality might involve the lifespan of osteocytes, which are long-lived but not immortal. We have demonstrated that chronic glucocorticoid administration to mice and humans increases the prevalence of osteocyte and osteoblast apoptosis.³ The proportion of apoptotic osteocytes is higher than that of apoptotic osteoblasts, which probably reflects the unique unavailability of osteocytes for phagocytosis (because of their anatomic isolation from scavenger cells) and the need for extensive cellular degradation before disposal through the narrow canaliculi. As a consequence, apoptotic osteocytes accumulate. As long as glucocorticoid treatment persists, the associated decrease in bone turnover makes this accumulation unrepairable. The osteocytes, their lacunae, and the connecting canalicular system form an extensive sensory network that monitors bone quality and can recruit osteoclasts and osteoblasts to repair defective bone. Disruption of the osteocyte–lacunar–canalicular network could compromise lacunocanalicular circulation, detection of microdamage, and transmission of signals that lead to bone repair. This disruption could result, therefore, in defective bone material properties and increased fragility of bone, independent of any changes in bone mass. In support of this contention, O'Brien *et al.* have blocked glucocorticoid action in osteoblasts and osteocytes by tissue-specific, transgenic expression of 11 β -hydroxysteroid dehydrogenase type 2, an enzyme that inactivates glucocorticoids.⁴ Prevention of osteocyte apoptosis in prednisolone-treated transgenic animals was associated with preservation of bone strength, despite similar losses of BMD in both wild-type and transgenic animals.

Angeli *et al.* have provided us with compelling evidence of a surprisingly high prevalence of asymptomatic vertebral fractures in a large cohort of postmenopausal women undergoing long-term glucocorticoid therapy. BMD determinations, bone ultrasound measurements, and quality-of-life questionnaires were ineffective for predicting the number or severity of the fractures; however, vertebral fractures are a strong risk factor for additional fractures, independent of BMD. Angeli *et al.* make a convincing case for vertebral fracture assessment in all patients who receive chronic glucocorticoid therapy. Vertebral morphological assessment with dual energy X-ray absorptiometry, spinal radiographs, or (at the very least) serial height measurements with a stadiometer might help to identify patients at risk of glucocorticoid-induced fracture. All patients found to be at risk should be treated with aminobisphosphonates

as soon as possible.⁵ Although serial BMD measurements might be clinically useful in the follow-up of patients on aminobisphosphonate therapy, they cannot be used to identify those at risk of glucocorticoid-induced osteoporosis.

PRACTICE POINT

The disparity between bone quantity and quality in glucocorticoid-induced osteoporosis makes BMD or ultrasound measurements inadequate for the identification of patients at risk of glucocorticoid-induced fractures

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