

REVIEW ARTICLE

Osteoporosis in the at-risk asthmatic

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To cite this article: Aljubran SA, Whelan GJ, Glaum MC, Lockey RF. Osteoporosis in the at-risk asthmatic. *Allergy* 2014; DOI: 10.1111/all.12438.

Keywords

asthma; bisphosphonates; glucocorticoids; osteoporosis.

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Accepted for publication 27 April 2014

DOI:10.1111/all.12438

Edited by: Douglas Robinson

Abstract

The effect of inhaled glucocorticosteroids (ICS) on bone metabolism and subsequent osteoporosis is controversial. Explanations for this controversy include various study designs, duration of use, outcome measures, and population demographics of research studies with intranasal or inhalational ICS. Patients with poorly controlled asthma are at greatest risk of osteoporosis because they are commonly treated with intermittent or continuous systemic corticosteroids (SCS) or high-dose ICS. A 45-year-old Caucasian woman presents with moderate-to-severe asthma with frequent albuterol use and nighttime awakenings at least once weekly. She is on fluticasone/salmeterol 500/50 µg one inhalation twice daily and montelukast 10 mg/day. She requires prednisone 15 mg three times per day for 5 days up to three times a year. Is this patient at greater risk of osteopenia, characterized by a T-score between -1.0 and -2.5 , and subsequent osteoporosis and an increased risk of fractures? If she has osteopenia, should she be treated with a bisphosphonate? The risk of osteoporosis and fracture increases significantly with frequent administration of SCS, and patients on such medications should undergo preventative measures and treatment. This study discusses factors that contribute to an increased risk of osteoporosis/osteopenia in patients with asthma and suggests recommendations based on the current literature.

Osteoporosis is a disease of the bone characterized by low bone mass, bone fragility, and increase risk of bone fracture (1). The World Health Organization (WHO) defines osteoporosis as a bone mineral density (BMD) value of more than 2.5 standard deviations below the mean for normal young adults while defining osteopenia as a BMD of more than 1 SD below the young adult mean, but <2 SD below this value (T-score <-1 and >-2.5) (1–3). In the United States and Europe, approximately 30% of all postmenopausal women and approximately 200 million people worldwide have osteoporosis (4). Asian and Hispanic women have the same prevalence of osteoporosis as White women. In the USA, Black women have lower prevalence of osteoporosis after adjusting for age and the rate of hip fracture is lower as well (1).

Annually, 1.5 million subjects with osteoporosis suffer from fractures related to this disease and have an 86% chance of subsequent fractures. Additionally, those who suffer a vertebral fracture have a 2.3-fold increased risk of a hip fracture and 1.4-fold increased risk of a distal forearm fracture (5, 6). Direct expenditures on osteoporotic fractures in 2002 are estimated to be \$17.9 billion annually. By 2020, estimates indicate that osteoporosis will affect 14 million

people and 47 million people over the age of 50 will have either osteoporosis or osteopenia in the United States (1).

According to the National Osteoporosis Foundation, all individuals over the age of 50 should be evaluated for osteoporosis risk factors (Table 1) (7). Bone mineral density testing is recommended for all women at the age of 65 and men at the age of 70 and older. Bone mineral density is recommended also for adults at the age 50 and greater if risk factors for osteoporosis are identified or there is a history of fracture after the age of 50 (7). Pharmacologic therapy such as a bisphosphonate is recommended if a BMD T-score is <-2.5 at the femoral neck, total hip, or spine. Bone mineral density by DXA scan is recommended every 2 years after initiating pharmacotherapy. In patients <50 years of age, Z-scores are more appropriate to use than T-scores to diagnose low bone density, as they account for age, race, gender, and weight (7).

Proposed mechanisms of glucocorticoid-induced osteoporosis

Glucocorticosteroids (GS) affect the trabecular more than cortical bone, most likely due to the greater amount of meta-

Table 1 Conditions, diseases, and medications that cause or contribute to osteoporosis and fractures

Lifestyle factors		
Low calcium intake	Vitamin D insufficiency	Excess vitamin A
High caffeine intake	High salt intake	Aluminum (in antacids)
Alcohol (3 or more drinks/day)	Inadequate physical activity	Immobilization
Smoking (active or passive)	Falling	Thinness (low BMIs)
Genetic factors		
Cystic fibrosis	Homocystinuria	Osteogenesis imperfecta
Ehlers-Danlos	Hypophosphatasia	Parental history of hip fracture
Gaucher's disease	Idiopathic hypercalciuria	Porphyria
Glycogen storage diseases	Marfan syndrome	Riley-day syndrome
Hemochromatosis	Menkes steely hair syndrome	
Hypogonadal states		
Androgen insensitivity	Hyperprolactinemia	Turner's and Klinefelter's syndromes
Anorexia nervosa and bulimia	Panhypopituitarism	
Athletic amenorrhea	Premature ovarian failure	
Endocrine disorders		
Adrenal insufficiency	Diabetes mellitus	Thyrotoxicosis
Cushing's syndrome	Hyperparathyroidism	
Gastrointestinal disorders		
Celiac disease	Inflammatory bowel disease	Primary biliary cirrhosis
Gastric bypass	Malabsorption	
GI surgery	Pancreatic disease	
Hematologic disorders		
Hemophilia	Multiple myeloma	Systemic mastocytosis
Leukemia and lymphomas	Sickle cell disease	Thalassemia
Rheumatic and autoimmune diseases		
Ankylosing spondylitis	Lupus	Rheumatoid arthritis
Miscellaneous conditions and diseases		
Alcoholism	Emphysema	Muscular dystrophy
Amyloidosis	End-stage renal disease	Parenteral nutrition
Chronic metabolic acidosis	Epilepsy	Post-transplant bone disease
Congestive heart failure	Idiopathic scoliosis	Prior fracture as an adult
Depression	Multiple sclerosis	Sarcoidosis
Medications		
Anticoagulants (heparin)	Cancer chemotherapeutic drugs	Gonadotropin-releasing hormone agonists
Anticonvulsants	Cyclosporine A and tacrolimus	Lithium
Aromatase inhibitors	Depo-medroxyprogesterone	
Barbiturates	Glucocorticoids (≥5 mg/day of prednisone or equivalent for ≥3 months)	

bolic activity in the former. This explains why DXA scans of the greater trochanter and lumbar spine are preferred to assess the degree of osteopenia versus osteoporosis. Chronic GC use also affects cortical bone density causing increased fragility of the long bones (8).

Glucocorticosteroids reduce proliferation and differentiation and increase apoptosis of bone-forming cells or osteoblasts. Synthesis of type I collagen and $\beta 1$ integrin is suppressed, while collagenase-3 (MMP-13) is increased, thus attenuating the ability of osteoblasts to form a matrix. Osteocalcin gene expression in osteoclasts, bone-absorbing cells, is also decreased by GC. However, osteoclast progenitors, bone-derived monocytes and macrophages, may be stimulated by GC to differentiate into mature osteoclasts (8). GC may also affect growth factors, cytokines, and prostanoids causing a skewed regulation of the local bone environment.

These include a decrease in insulin-like growth factors (IGF-I, II), IGF-binding proteins, hepatocyte growth factor (HGF), and prostaglandin E₂ (PGE₂) (8).

Inhaled corticosteroids and osteoporosis/fractures

Inhalational corticosteroids have lower bioavailability compared with systemic corticosteroids (SCS). Therefore, high-dose ICS for prolonged periods, especially in at-risk patients, may pose a problem and increased the incidence of osteopenia/osteoporosis.

Wong et al. (9) performed a retrospective study in the United Kingdom to determine whether ICS affected BMD, independent of confounding factors such as physical activity and SCS use. One hundred and ninety-six subjects (61% women) taking a wide range of daily doses of beclometha-

sone dipropionate, budesonide, or fluticasone propionate were recruited. The majority of participants were prescribed SCS in the past. A negative linear association was observed between log of cumulative doses of ICS to all BMD measurements (lumbar, femur neck, trochanter, and Ward's triangle). Adjusting for age and sex, the doubling in the cumulative dose of ICS resulted in a decrease in BMD at the lumbar spine of 0.023 g/cm^3 (95% CI 0.005–0.041) or 0.16 SD (0.04–0.28). Similar effects were observed at other scanned sites (Fig. 1) (9).

Patients with mild asthma were randomized in another open-label prospective study to receive ICS or a nonsteroidal therapy for 2 years and were monitored for changes in BMD. The trial consisted of three treatment arms: budesonide, beclomethasone dipropionate, or a nonsteroidal treatment. Participants were allowed up to three SCS 'bursts'. BMD was measured at baseline and at 6, 12, and 24 months. The mean dose of ICS correlated with a decrease in lumbar spine BMD ($P < 0.01$) at 24 months. Biomarkers of bone metabolism, for example serum osteocalcin, urinary deoxypyridinoline, and pyridinoline, were not correlated with changes in BMD. This study hallmarks significant changes in bone density, which were thought not to be clinically important, in participants who use relatively low daily doses ($<500 \text{ µg/day}$) of ICS (10).

The HUNT-2 (Nord-Trøndelag Health) is a multicenter, open-label observational longitudinal study that incorporated

a substudy, the Bronchial Obstruction in Nord-Trøndelag Study (BONT) (11). Bone mineral measurements and spirometry were performed in 10 941 participants. At follow-up, 2848 completed the study and 23% were on ICS daily doses $>800 \text{ µg}$ of budesonide, beclomethasone dipropionate, or fluticasone propionate. Fifty-eight percent (373) were taking a fluticasone propionate and salmeterol combination medication. A significant decrease in BMD (-0.88 mg/cm^2 , $P < 0.01$) occurred in the groups taking ICS with exposure to SCS compared to the group with no exposure to ICS or SCS (Fig. 2) (11).

Since the late 1970s, asthma mortality in the United States steadily increased, hitting a peak in 1999 ($1.7 : 100\,000$) (12). Mortality began to decline to $1.1 : 100\,000$ in 2009 with the introduction of ICS and LABA therapy used in the same device (13). There are three combination therapies available in the USA: fluticasone propionate (100, 200 or 500 µg) and salmeterol (50 µg) (Advair® Diskus®; Glaxo SmithKline, London, UK) (Advair® MDI is also available at different doses), budesonide (80 or 160 µg) and formoterol (4.5 µg) (Symbicort® MDI; AstraZeneca, London, UK), and mometasone furoate (100 or 200 µg) and formoterol (5 µg) (Dulera® MDI; Merck, Whitehouse Station, NJ, USA). There are few studies examining the effect of ICS/LABA combination therapy on bone metabolism. One study by Pasaoglu et al. investigated the risk of osteoporosis in patients with asthma taking

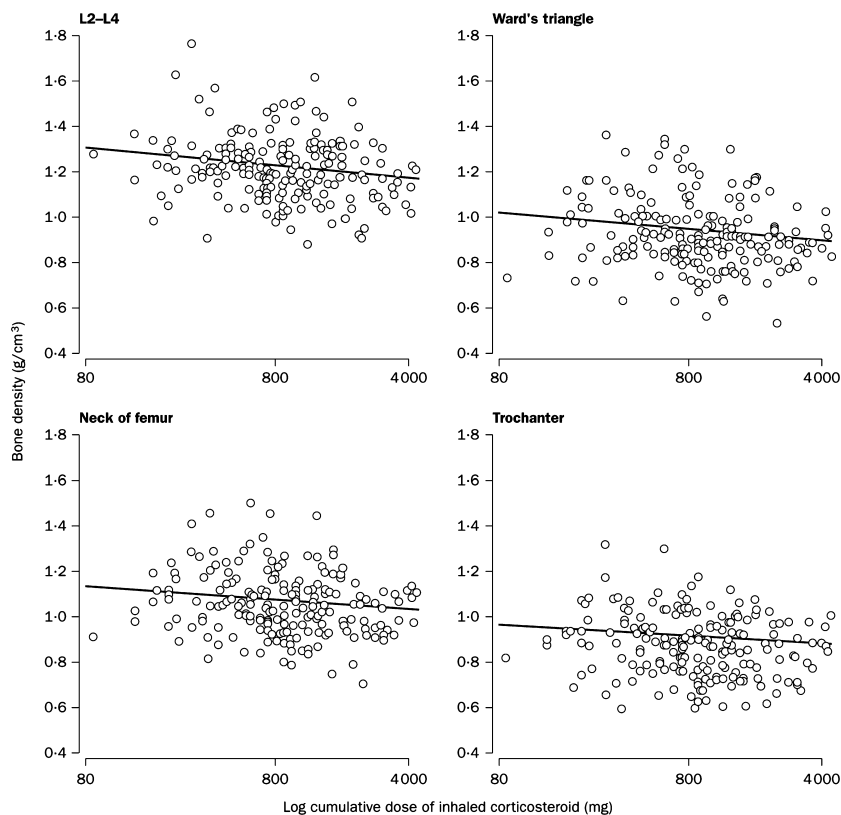


Figure 1 Cumulative dose of inhaled glucocorticosteroids (ICS) and bone mineral density (BMD) Reproduced from (9). Reprinted from *The Lancet*, Vol. 355, Wong et al., 'Inhaled corticosteroid use and bone-mineral density in patients with asthma', Pages 1399–1403, Copyright 2000, with permission from Elsevier.

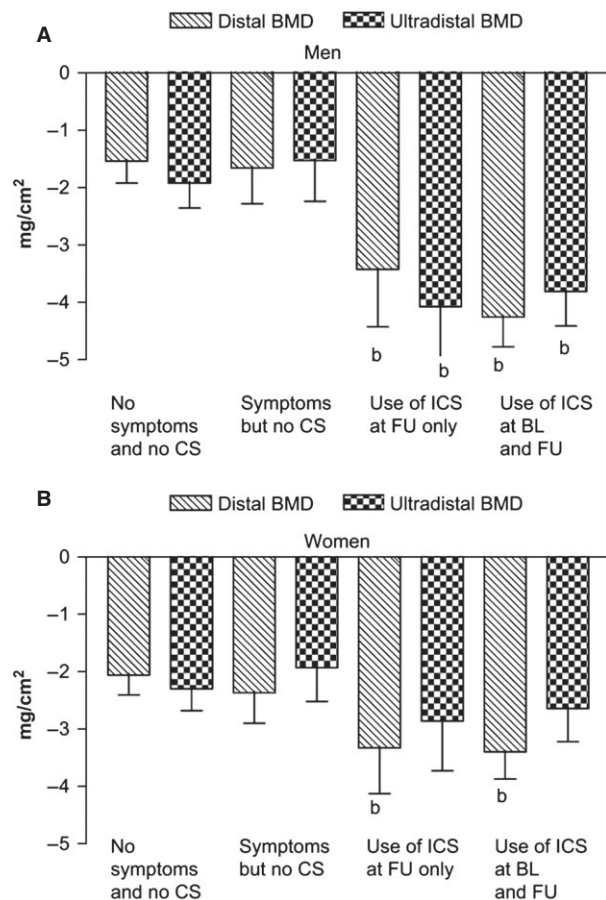


Figure 2 Mean yearly loss of distal and ultradistal bone mineral density (BMD) by symptom and use of inhaled glucocorticosteroids (ICS) among men (A) and women (B) compared to the group with no symptoms and no ICS use. CS, corticosteroids; FU, follow up; BL, baseline; $b < 0.01$ (Reproduced from (11). This article was published in *Respiratory Medicine*, Vol. 101, Langhammer et al., 'Effect of inhaled corticosteroids on forearm bone mineral density: The HUNT Study, Norway', Pages 1744–1752, Copyright Elsevier (2007).

fluticasone plus salmeterol or budesonide plus formoterol therapy delivered by two separate devices. Combination therapy was compared to ICS monotherapy (fluticasone propionate, budesonide, and beclomethasone dipropionate) for a period of 1 year. The BMD with DXA scanning of the lumbar spine and femoral neck was performed at baseline and in 1 year (14). Forty-three participants completed the study. The average daily ICS doses for the combination and monotherapy arms were 543 μg and 920 μg , respectively. No significant BMD changes occurred in any of the DXA sites with these two different treatment modalities (14).

Coadministration of an ICS plus a LABA in one device may have a synergistic effect on lung function (15). Large-scale trials with ICS and LABA combination in a single inhaler are needed to determine the effect on BMD and fracture risk as ICS/LABA combinations are currently the most popular mode of pharmacotherapy in patients with persistent asthma. The Towards a Revolution in COPD Health

(TORCH) trial is a 3-year study of fluticasone (500 μg), salmeterol (50 μg), or a combination of the two (Advair® Disks®) (500/5 μg) in which participants with COPD were monitored for the improvement of their disease. BMD data were collected prospectively and reported in a separate analysis (16). The analysis found that despite the high prevalence of osteoporosis in the study population, the treatment administered had no significant effect on the BMD when compared with placebo (16). Although this trial did not investigate combination therapy in asthma, it does provide evidence that the BMD is not affected, at least for the duration of the study, in patients with COPD.

Patients on ICS/LABA combination therapy are exposed to β_2 agonist and ICS on a continual basis. The potential for central mechanisms responsible for bone modeling has been proposed. Centrally acting signaling molecules, such as neuropeptide Y (Y1, Y2), endocannabinoids (CB1, CB2), dopaminergic, serotonergic, β adrenergic receptors, nitric oxide synthase (NOS) enzymes, and receptor activator of nuclear factor- κB ligand (RANKL), are implicated in bone remodeling. β_2 receptors, which are balanced by the effects of leptin, are expressed on osteoblasts and implicated in the modulation of sympathetic tone. Blocking β_2 receptors may result in an increased bone mass (17), a relationship that suggests that constant stimulation of the β_2 receptor by LABAs may pose a risk for the development of osteoporosis. Therefore, theoretically, β_2 agonist use may affect bone architecture in asthmatics, especially in children. Early and continuous use of these agents could potentially initiate a cascade of cellular and tissue events that predispose to osteoporosis.

Exercise, calcium supplementation, and bone mass

Weight-bearing exercise is necessary in patients at risk of osteoporosis, whereas aerobic exercise, for example treadmill exercise, alone is not sufficient to preserve bone mass (18, 19). In a prospective, 2-year trial, an exercise program was designed to target women in the early stage of postmenopause (20). The 24-month program consisted of high-impact aerobic exercise in an attempt to maintain bone mass in the proximal femur and spine. Those who participated had significant benefit. High-impact exercise induces growth hormone production, and the mechanical forces cause transient microdestruction of bone and stimulate bone formation. Results from this study indicate that a prescribed exercise program should be individualized for each patient based on the tolerable exercise level, in particular, for patients at risk of osteoporosis such as those on ICS or SCS (21). The exercise-induced gain in BMD may not persist after exercise cessation. A study was performed in 34 elderly women (18 exercisers and 16 controls) who were invited for a 5-year follow-up assessment for BMD after the 12-month intervention. The 5-year follow-up assessment of BMD after exercise cessation showed that both groups had a significant decrease in BMD (22).

A diet rich in calcium and vitamin D is important, especially with advancing age. Vitamin D deficiency is associated with poor lung function and a decrease in response to GC; thus, vitamin D supplementation may be crucial in patients

with asthma (23). Timing of the day is important in calcium supplementation; 500 mg of calcium is the maximum that the body can absorb at one time. Supplementation of calcium can be split in a 1 : 2 ratio from morning until evening (24). Vitamin D is necessary for calcium absorption. Therefore, calcium supplements should contain between 400 and 800 IU of vitamin D. Calcium carbonate, an inexpensive supplement, is best absorbed when taken with food, while calcium citrate does not require food for adequate absorption (25, 26). Calcium citrate has claims of better absorption compared with calcium carbonate and is absorbed better in a nonacidic environment. Calcium formate is a newer formulation and has impressive bioavailability in pharmacokinetic studies (27, 28).

Calcium intake and increased risk of cardiovascular disease (CVD) were investigated in several studies. The data are conflicting (29). A prospective study published in JAMA included 388 229 subjects during the 12-year duration of the study. The authors concluded that high intake of calcium supplements is associated with an increased risk of CVD death in men and not in women (30). Other studies showed no risk.

Another concern with calcium intake is kidney stone formation. Studies suggest that dietary calcium is associated with lower incidence of kidney stones, while exogenous calcium supplementation may be associated with increased risk of kidney stones (31, 32).

Concomitant pharmacologic therapy affecting BMD

Various medications negatively affect BMD. These include calcineurin inhibitors (cyclosporine, tacrolimus, and pimecrolimus), levothyroxine, medroxyprogesterone, luteinizing hormone-releasing hormone (LHRH) agonists, aromatase inhibitors (anastrozole, letrozole, and vorozole), heparin, neuroleptics (phenothiazine, haloperidol, and droperidol), anticonvulsants (phenytoin and phenobarbital) methotrexate, diuretics, phosphate-binding agents (aluminum), orlistat, and proton-pump inhibitors (PPIs) (33, 34). Smoking and chronic ethanol consumption also affect BMD (33).

Proton-pump inhibitor use may be a risk for potential osteoporotic effects. Long-term studies demonstrate that their use increases the risk of osteoporosis-related fractures. This is important because of the comorbid association of GERD with asthma. Proposed mechanisms include a pH-dependent decrease in oral bioavailability of calcium and an effect on the H⁺/ATPase transporter in osteoclast cell membranes (34). Targownik et al. demonstrated in a retrospective cohort study that the use of PPIs for 5 years was associated with increased hip fractures. The risk was highest after seven or more years of exposure (35). These findings are consistent with previous results by Yang et al. (36).

The 'statin' class (3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors) is under investigation for their possible positive BMD benefits. Simvastatin, for example, decreases osteoclast differentiation and interrupts the NF- κ B pathway associated with osteoporosis via inhibition of RANKL (37). Clinical trials provided mixed results (38, 39); thus, statins are not presently recommended to prevent or treat osteoporosis.

Medications that strongly affect the metabolic enzymes for ICS also should be considered. Ritonavir, a protease inhibitor used to treat HIV, inhibits the cytochrome P450 (CYP 3A4) enzyme. Ritonavir potentiates the effect of fluticasone propionate by increasing its bioavailability and thus could lead to more systemic side effects. This interaction could provide one explanation as to why Cushing's syndrome is potentiated in patients with HIV infection taking this medicine (40). Many other potential interactions between ICS and CYP3A4 inhibitors, for example clarithromycin and itraconazole, are reported (41, 42).

As newer formulations of ICS become available, such as ciclesonide and fluticasone furoate, some may pose a greater potential to affect bone metabolism. Published studies are not available on bone metabolism or fracture incidence with these ICS formulations. However, with increased ICS localized potency and better aerosol delivery device design, the systemic impact of these medications theoretically should decrease.

Bisphosphonates, inhaled corticosteroids, and osteoporosis

There are three generation classes of bisphosphonate. The length, size, and orientation of the incorporated nitrogen and potency in the organic side chains that spans four orders of magnitude are key properties that determine potency (43, 44). The proposed mechanism of action is interruption of osteoclast vacuolar H⁺-ATPase and inhibition of HMG-CoA reductase. This interaction affects the mevalonate pathway and ultimately leads to a decrease in osteoclast recruitment and activity and promotes osteoclast apoptosis (44).

There are seven USA Federal Drug Administration-approved bisphosphonates: pamidronate, tiludronate, etidronate, alendronate, risedronate, ibandronate, and zoledronic acid. The last four (Table 2) are approved for the prevention and/or treatment of osteoporosis in postmenopausal women.

The prophylactic bisphosphonate use in perimenopausal women on high doses of ICS was investigated in a small clinical trial by Lau et al. Chinese women with asthma who were pre- or postmenopausal on 800–1600 μ g/day of ICS were randomized to receive either 10 mg daily of alendronate or placebo for 1 year. Women in the treatment group demonstrated an increase in BMD in the femoral neck ($P < 0.05$), intertrochanteric area ($P < 0.01$), and total hip ($P < 0.001$) when compared to placebo (45). This is a relatively small trial ($n = 100$, 41 premenopausal) and of short duration (1 year), using alendronate 10 mg daily. Therefore, it is unclear whether these results are applicable to the usual 35 mg weekly dose of alendronate to prevent osteoporosis. In another Finnish study, peri- and postmenopausal women (and men) who had asthma and were on GC and ICS were randomized to receive clodronate IM injections, or placebo for 1 year. The group treated with 2400 mg/day of clodronate demonstrated an increase in BMD at the lumbar spine ($P < 0.01$), femoral neck ($P < 0.0001$), and intertrochanteric areas ($P < 0.02$) (46).

Campbell et al. conducted a five-year, open-label, multicenter, randomized, parallel-group study where osteoporotic

Table 2 Bisphosphonates indicated by the FDA for the prevention and treatment of osteoporosis

Drug	Trade name	FDA indications	Dosing	Dosage form	Manufacturer
2nd Generation					
Alendronate sodium	Fosamax®	Treatment and prevention of osteoporosis in postmenopausal women Treatment to increase bone mass in men with osteoporosis Treatment of glucocorticoid-induced osteoporosis in men and women Treatment of Paget's disease of bone in men and women	Treatment of osteoporosis in men and women: 10 mg tablet daily, 70 mg (tablet or solution) weekly Prevention of osteoporosis in men and women: 35 mg tablet once weekly, or 5 mg tablet once daily Treatment of glucocorticoid induced osteoporosis: 5 mg daily (10 mg daily for postmenopausal women not on estrogen) Treatment of Paget's disease 40 mg daily for 6 months.	5, 10, 35, 40, 70 mg tablets 70 mg/75 ml raspberry flavored solution	Merck & Co., Inc., Whitehouse Station, NJ
Ibandronate sodium	Boniva®	Treatment and prevention of osteoporosis in postmenopausal women	150 mg once monthly	150 mg tablet	Genentech USA Inc./ Roche, South San Francisco, CA
3rd Generation					
Zoledronic acid	Reclast®	Treatment of osteoporosis Treatment and prevention of glucocorticoid-induced osteoporosis Treatment of Paget's disease of bone in men and women	5 mg per year	5 mg/100 ml infusion	Novartis Pharmaceuticals Corporation, East Hanover, NJ
Risedronate sodium	Actonel®	Treatment and prevention of postmenopausal osteoporosis Treatment to increase bone mass in men with osteoporosis Treatment of glucocorticoid-induced osteoporosis Treatment of Paget's disease	Treatment of post menopausal osteoporosis: 5 mg daily, 35 weekly, 75 mg for 2 days once a month, or 150 mg once a month Prevention of postmenopausal osteoporosis 5 mg daily, 35 mg weekly Men with osteoporosis: 35 mg weekly Glucocorticoid induced osteoporosis: 5 mg daily Paget's disease: 30 mg daily for 2 months	5, 30, 35, 75, 150 mg tablets	Warner Chilcott (US), LLC, Rockaway, NJ

changes were examined in 349 postmenopausal women who had been taking ICS with or without concomitant GC. Participants were given either etidronate, calcium, etidronate with calcium, or no treatment for 1 year. BMD was measured by DXA scan at baseline and annually thereafter. Fracture rates were reduced in participants who did not have a prior history of an osteoporotic fracture compared with those who did have such a fracture (−9.4%) ($\chi^2 = 4.2$, $P = 0.04$). In the group treated with etidronate, the change in BMD of the lumbar spine at 5 years was significant at 4.1% (95% CI = 2.0–6.2), whereas calcium supplementation did not show a significant change even as part of the etidronate regimen (47).

The mean increase in BMD from baseline of the lumbar spine was significantly greater in the alendronate arm (4.9%,

$P = 0.0005$) compared with alfacalciferol (1- α -hydroxyvitamin D(3)) arm ($P = \text{NS}$) at 12 months in a double-blinded, randomized trial conducted in Japan comparing these two medications in postmenopausal asthmatic women on ICS (48).

The FDA has raised concerns about the possible association of bisphosphonate with long-term use with atypical subtrochanteric and diaphyseal femur fractures. The FDA and the American Society of Bone and Mineral Research's (ASBMR) expert Task Force are cooperating to monitor for such an association. The FDA recommends that patients taking bisphosphonates who have the onset of thigh pain report to their healthcare professional immediately.

Several studies related to this issue have been published since the FDA warning and are reviewed by Schilcher et al.

in the NEJM 2011 (49). The authors conclude that the prevalence of bisphosphonate use among patients with atypical fractures was increased although the risk was considered to be small. The same group concluded in a 2013 study that stress fractures of the femur shaft are strongly related to bisphosphonate use (50). Park-Wyllie et al. explored the long-term association of bisphosphonate treatment with atypical femur fractures (subtrochanteric or femoral shaft) in another large, Canadian, nested case-controlled study. Women who used bisphosphonates for 5 years or longer were at increased risk for hospitalization from a subtrochanteric or femoral shaft fracture compared with transient (<100 days) use (adjusted OR, 2.74; 95% CI 1.25–6.02). Shorter durations of bisphosphonate use (<5 years to 100 days) were not associated with this fracture risk. Expectedly, overall fracture risk was decreased in women taking long-term bisphosphonates (51). The authors note a low absolute risk associated with the use of bisphosphonates beyond 5 years; 0.13% in the first subsequent year and 0.22% within 2 years. Overall, concomitant medication use was greater in the atypical fracture group compared with the control group, and the atypical femur fracture group had a 10% greater use in PPIs resulting in the recommendation that the patient's medication be reviewed and possibly changed before making alterations in bisphosphonate therapy.

Other unsuspected adverse events associated with bisphosphonate use also are reported, such as osteonecrosis of the jaw. In a review of 2400 cases, 88% of the cases of bisphosphonate-induced osteonecrosis of the jaw were associated with the intravenous use of the bisphosphonate, zoledronate, and 89% were associated with treatment of a malignant condition (52). Esophageal cancer also has been observed in patients taking bisphosphonates. In 2009, the FDA reported on 23 cases of patients diagnosed with esophageal cancer (53). In a study by Green et al., 2954 patients above the age of 40 years with esophageal cancer were included. A higher risk of esophageal cancer was associated with age >80 years old (44% incidence) and with more than 3 years of bisphosphonate use (RR 2.24 [1.47–3.43]) (54). Increased risk of atrial fibrillation was reported with bisphosphonate use in a study dubbed the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial, but further investigation is required to determine whether such an association exists (55).

The American College of Rheumatology (ACR) made recommendations regarding bisphosphonate use in patient starting GC therapy. The Fracture Risk Assessment (FRAX) Tool, developed by WHO task force in 2008, is used to calculate the risk. This tool though is not applicable in the calculation for fracture risk in premenopausal women or men younger than age 40 years. Subjects who are at risk of fracture are grouped into three categories as per the ACR: low, medium, and high.

The recommendations for postmenopausal women and men of 50 years or older are as follows. A bisphosphonate is not recommended in low risk subjects with prednisone doses of ≤ 7.5 mg/day. Alendronate, risedronate or zoledronic acid is recommended in low risk subjects for prednisone dose

≥ 7.5 mg/day if taken for ≥ 3 months. Alendronate, risedronate or zoledronic acid is recommended in medium risk subjects if the prednisone dose is ≥ 7.5 mg/day for ≥ 3 months. Alendronate, risedronate, zoledronic acid or teriparatide is recommended in high risk subjects with prednisone dose ≥ 5 mg/day for ≤ 1 month or any dose of prednisone for ≥ 1 month (Table 3) (56).

The ACR recommendations for bisphosphonate therapy in premenopausal women and men younger than 40 years of age were made only for those with a history of a prevalent fragility fracture (a fracture from a minor injury) who are at higher risk for additional fractures.

The following recommendations are made for such subjects: alendronate or risedronate is recommended for nonchildbearing subjects if receiving prednisone ≥ 5 mg/day for a period of 1–3 months. Zoledronic acid is recommended if receiving prednisone ≥ 7.5 mg/day for a period of 1–3 months. Alendronate, risedronate, zoledronic acid or teriparatide is recommended for nonchildbearing subjects with prednisone for ≥ 3 months. Alendronate, risedronate or teriparatide is recommended for potential childbearing subjects with prednisone ≥ 7.5 mg/day for ≥ 3 months (Table 4) (56).

Table 3 American College of Rheumatology pharmacological recommendations for postmenopausal women and men ≥ 50 years starting GC therapy with an anticipated duration of ≥ 3 months or prevalent glucocorticosteroid therapy of at least 3 months (unless otherwise noted)*

Recommendations	Level of evidence
Low-risk patient	
Alendronate for ≥ 7.5 mg/day prednisone OR	A
Risedronate for ≥ 7.5 mg/day prednisone OR	A
Zoledronic acid for ≥ 7.5 mg/day prednisone	B
Medium-risk patient	
Alendronate for any dose of glucocorticoids OR	A
Risedronate for any dose of glucocorticoids OR	A
Zoledronic acid for ≥ 7.5 mg/day prednisone	B
High-risk patient†	
Alendronate OR	A
Risedronate OR	A
Zoledronic acid OR	B
Teriparatide‡	B

*Table modified from (56), Grossman et al., Arthritis Care and Research, © 2010 by the American College of Rheumatology. Published by John Wiley and Sons Ltd.

†Any anticipated dose or duration of glucocorticoids justifies initiating prescription therapy for high-risk patients.

‡For ≥ 5 mg/day prednisone with a duration ≤ 1 month and for any dose of glucocorticoids with a duration >1 month.

Other pharmacologic options

Strontium ranelate (57, 58), sodium fluoride, anabolic steroids, calcitriol, teriparatide (Forteo®; Eli Lilly and Company, Indianapolis, USA); parathyroid hormone [1–84]; and tibolone and selective estrogen receptor modifiers (SERMs includes raloxifene, Evista®; Eli Lilly and Company, Indianapolis, IN, USA) are examples of nonbisphosphonate modes of therapy demonstrated to have significant benefit for the treatment of osteoporosis. Lasofoxifene and bazedoxifene are next-generation SERMs that decrease fracture rates in postmenopausal women (59, 60). In 2013, bazedoxifene was approved in the USA, in combination with conjugated estrogens (Duavee™ conjugated estrogens 0.45 mg/bazedoxifene 20 mg; Pfizer, New York, NY, USA) for the prevention of postmenopausal osteoporosis. In the EU, bazedoxifene is licensed as Conbriza (Ligand Pharmaceuticals, La Jolla, CA, USA) and indicated for the prevention and treatment of osteoporosis in postmenopausal women. These therapeutic options are typically implemented when a patient has a sub-optimal response to a bisphosphonate. The concern of developing cancer prompted the European Medicines Agency (EMA) in 2012 to not recommend use of calcitonin for osteoporosis. In 2013, the FDA panel determined that the risk of

calcitonin to treat osteoporosis outweighs its benefits in postmenopausal women.

Hormone replacement therapy (HRT) is another method to prevent osteoporosis and fractures in peri- and postmenopausal women. However, there are concerns about an increased incidence of cancer and cardiovascular complications when taken for prolonged periods. Majoribanks et al. (61) conducted a comprehensive review on the long-term use of HRT in peri- and postmenopausal women. They determined that HRT did decrease the risk of bone fractures; however, because of the increased risks of cardiovascular, cerebrovascular, breast cancer, and gall bladder diseases, the risks outweigh the benefits.

Denosumab (Prolia®; Amgen Inc., Thousand Oaks, CA, USA) is a fully humanized monoclonal antibody approved for osteoporosis treatment in postmenopausal women who are at high risk of fractures. Denosumab inhibits the action of RANKL, a major regulator of osteoclasts (62). There are no studies using this drug in patients with asthma on ICS. However, denosumab was investigated in patients with rheumatoid arthritis taking GC. Bone mineral density increased at both the lumbar spine and total hip ($P < 0.001$) after 1 year of treatment, regardless of exposure to either GS or bisphosphonates (Fig. 3) (63).

Sclerostin is a glycoprotein that interferes with osteoblast function. Romosozumab is a monoclonal antibody against sclerostin, currently undergoing clinical trials. McClung et al. (64) investigated romosozumab in postmenopausal women. Individuals randomized to 140 or 210 mg of romosozumab monthly demonstrated significantly better BMDs at the lumbar spine, total hip, and femoral neck, when compared to placebo.

Table 4 Recommendations for premenopausal women and men under age 50 years with a history of fragility fracture*

Recommendations	Level of evidence
1–3 Months of glucocorticoids	
Nonchildbearing potential	
Alendronate if receiving prednisone ≥ 5 mg/day	A
OR	
Risedronate if receiving prednisone ≥ 5 mg/day	A
OR	
Zoledronic acid if receiving prednisone ≥ 7.5 mg/day	B
Childbearing potential—Inadequate data for recommendation	
≥ 3 Months of glucocorticoids	
Nonchildbearing potential	
Alendronate for any dose	A
OR	
Risedronate for any dose	A
OR	
Zoledronic acid for any dose	B
OR	
Teriparatide for any dose	B
Childbearing potential	
Alendronate if prednisone ≥ 7.5 mg/day	A
OR	
Risedronate if prednisone ≥ 7.5 mg/day	C
OR	
Teriparatide if prednisone ≥ 7.5 mg/day	C

*Table modified from (56), Grossman et al., Arthritis Care and Research, © 2010 by the American College of Rheumatology. Published by John Wiley and Sons Ltd.

Summary of bisphosphonate indications in patient initiating SCS

Patients who will initiate SCS therapy should be evaluated for osteoporotic fracture risk, lifestyle modifications, and possible treatment with bisphosphonate. The ACR categorizes patients into three categories: low, medium, or high risk based on the risk of a major osteoporotic bone fracture. The FRAX calculator can be used to define risk category considering the limitations mention earlier. The ACR recommendations vary based on the age, fracture risks, and the duration of SCS use. Postmenopausal women and men ≥ 50 were consider as one group, while premenopausal women and men younger than 50 were grouped together. All patients should be monitored while taking SCS.

Bisphosphonate therapy is recommended for postmenopausal women and men above the age of 50 if they are in a low-risk category and taking a dose of prednisone equivalent to 7.5 mg/day or more for 3 months or longer. Bisphosphonate therapy is recommended for any dose of prednisone use for 3 months or longer for the same group with medium risk of this disease. Bisphosphonate therapy is recommended for high-risk patients from the same group with any dose of prednisone regardless of duration.

There are no recommendations due to limited data for premenopausal women and men younger than 50 years without

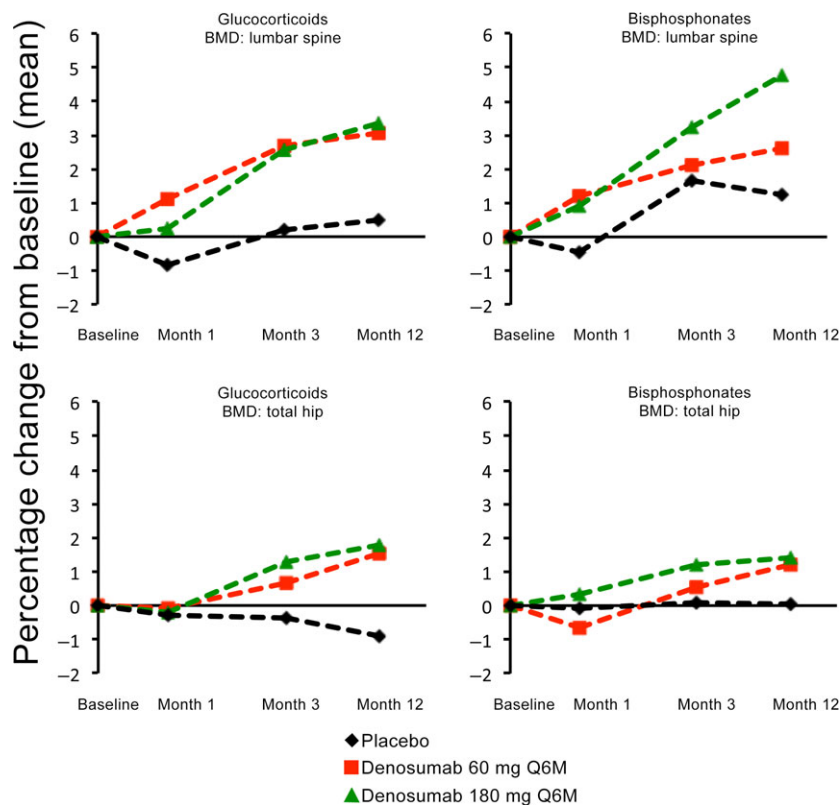


Figure 3 Bone mineral density and turnover: Glucocorticoid vs. Control (Modified from [63]. Reproduced from *Annals of the Rheumatic Diseases*, Dore et al., Vol.69, Pages 872-875, © 2014 BMJ Publishing Group Ltd & European League Against Rheumatism with permission from BMJ Publishing Group Ltd)

a prevalent fragility fracture who are prescribed SCS therapy. The ACR suggests that this area needs further research.

Bisphosphonate therapy is recommended for nonchildbearing aged women or men <50 years with a prevalent fragility fracture when prescribed prednisone ≥ 5 mg/day or more for 1 month or longer.

There is no consensus for women of childbearing age with a prevalent fragility fracture taking prednisone for ≤ 3 months, although bisphosphonate therapy is recommended for a prednisone dose of ≥ 7.5 mg/day for more than 3 months.

Conclusions

Perimenopausal women on high doses of ICS with the occasional use of SCS may benefit from prophylactic bisphosphonate therapy. Given the rare risk of bisphosphonate-associated femur fractures, patients and clinicians alike should monitor bisphosphonate use. At-risk patients for osteopenia/osteoporosis should be attentive to their diet,

weight-bearing exercises, and modifiable risk factors. Drug therapies, for example PPIs and others, which can directly accelerate osteoporosis, should be prescribed only if the risk/benefit justifies their use. Postmenopausal women and men ≥ 50 on GC therapy should be evaluated for fracture risk using the FRAX tool. Bisphosphonate therapy can be prescribed based on the fracture risk category as per the ACR recommendations. In patients who are unable to take bisphosphonates, or who are unresponsive to therapy, referral to a subspecialist, such as a rheumatologist or endocrinologist, should be considered. Novel treatments, such as denosumab and others, are now available and may provide therapeutic alternatives to bisphosphonate therapy.

Conflicts of interest

Glenn Whelan is currently employed by Genentech, USA (a member of the Roche group). The rest of the authors declare no conflict of interest.

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