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The Skeletal Effects of Inhaled Glucocorticoids

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Abstract The skeletal effects of inhaled glucocorticoids are poorly understood. Children with asthma treated with inhaled glucocorticoids have lower growth velocity, bone density, and adult height. Studies of adults with asthma have reported variable effects on BMD, although prospective studies have demonstrated bone loss after initiation of inhaled glucocorticoids in premenopausal women. There is a dose-response relationship between inhaled glucocorticoids and fracture risk in asthmatics; the risk of vertebral and non-vertebral fractures is greater in subjects treated with the highest doses in the majority of studies. Patients with COPD have lower BMD and higher fracture rates compared to controls, however, the majority of studies have not found an additional detrimental effect of inhaled glucocorticoids on bone. While the evidence is not conclusive, it supports using the lowest possible dose of inhaled glucocorticoids to treat patients with asthma and COPD and highlights the need for further research on this topic.

Keywords Osteoporosis · Fracture · Glucocorticoids · Inhaled steroids · Pulmonary disease

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Introduction

While the deleterious effects of oral and intravenous glucocorticoids on bone are well recognized, far less is known about whether and to what extent inhaled glucocorticoids have skeletal consequences. Given the prevalence and often chronic nature of inhaled glucocorticoid use, it is important to understand the potential adverse effects of these medications. There are currently close to 40 million people with asthma and chronic obstructive pulmonary disease (COPD) in the USA, and the prevalence of these diseases is rising [1–4]. Over 10 million individuals with asthma use inhaled glucocorticoids [5–7]. Although inhaled glucocorticoid use is more intermittent among COPD patients, approximately 39–50 % report some use of these medications [8].

Glucocorticoid-induced osteoporosis, specifically related to oral and intravenous glucocorticoids, is the most common secondary cause of osteoporosis. These medications profoundly decrease bone formation by decreasing osteoblast number and function, both inhibiting differentiation and increasing apoptosis [9, 10]. They reduce osteocyte viability, and may adversely affect osteocyte function by increasing the size of osteocyte lacunae, and decrease the mineralization and strength of the surrounding bone [10–12]. Systemic glucocorticoids may also adversely affect the bone through increased urinary calcium losses, decreased intestinal calcium absorption, and hypogonadism [13]. Bone loss and fracture risk are directly associated with dose and duration of use [14, 15] and occur as early as 3 to 6 months after initiation of oral glucocorticoid therapy [16]. Patients who use oral glucocorticoids have a greater risk of fracture than untreated individuals who have similar areal bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) [17]. This finding suggests that factors other than areal BMD are important determinants of fragility in glucocorticoid-treated patients.

Recent work has demonstrated that postmenopausal women using oral glucocorticoids have lower volumetric BMD, worse microarchitecture, and lower strength by high resolution peripheral CT compared to controls despite similar areal BMD by DXA [18].

Whether the effects of inhaled glucocorticoids differ from those of oral and intravenous glucocorticoids is not known. Although systemic absorption with inhaled glucocorticoids is less than oral glucocorticoids, it does occur. After inhalation, 80–90 % of the inhaled glucocorticoid dose is swallowed and inactivated by hepatic first pass metabolism. The remaining 10–20 % enters the lung, where it acts locally and then is absorbed into systemic circulation [19]. The newer generation inhaled glucocorticoids have higher potency with stronger affinity for glucocorticoid receptors in the lungs, thus contributing to increased absorption through the pulmonary circulation. Several studies of commonly prescribed inhaled glucocorticoid medications have documented measurable serum levels after administration. Therefore, through systemic absorption, IGCs could result in potentially similar effects to oral and intravenous glucocorticoids. Some studies that have compared the effects of both oral and inhaled glucocorticoids have found lower fracture rates in inhaled glucocorticoid-treated subjects, although others have found similar effects with either therapy [20–24]. Comparisons of the two therapies are limited because of overlap between groups.

This update will review the most recent research into the skeletal effects of inhaled glucocorticoid therapy on bone health for patients with asthma and COPD and highlight the gaps in our existing knowledge. Several factors are important to consider when interpreting the available literature on the skeletal effects of inhaled glucocorticoids. Several studies have combined patients with asthma and COPD. This confounds the results as COPD has independent skeletal effects [25, 26]. Adherence to inhaled glucocorticoids is a common issue [27]. Most data is observational, and there are very few randomized clinical trials. Often patients who use inhaled glucocorticoids also receive intermittent oral or even intravenous glucocorticoids complicating interpretation of the results. Changes in health and mobility with initiation of inhaled glucocorticoid treatment can also confound results.

Effects of Inhaled Glucocorticoids on Fracture in Studies Combining Subjects with Asthma and COPD

Several large systematic analyses have studied the effects of inhaled glucocorticoids on bone in populations that included both asthma and COPD patients with conflicting results. Jones et al. evaluated in patients treated for 2 to 3 years with conventional treatment doses of inhaled glucocorticoids [28]. They found no increase in risk of vertebral fractures. This finding was supported by a case-control study by de Vries et al., which found no increase in hip or femur fracture risk in COPD and asthma patients using inhaled glucocorticoids after controlling for disease severity and use of oral glucocorticoids [20].

Several authors have found a dose-response relationship between inhaled glucocorticoid use and fracture risk. In a nested case control study, Suissa et al. did not find an increased risk of upper extremity or hip fracture in elderly subjects using inhaled glucocorticoids in low doses [29]. However, the risk of upper extremity fractures increased by 12 % with every 1000 μg increase in daily inhaled glucocorticoid dose. In subjects followed for more than 8 years, increased risk of hip fracture was seen in those using daily doses of over 2000 μg (RR 1.61, 95 % CI 1.04–2.50). Similarly, a population-based case-control study observed a small but significant increase in hip fractures in IGC users (OR 1.19, 95 % CI 1.10–1.28) after adjusting for oral glucocorticoid courses as well as a greater risk at higher doses [30]. A longitudinal cohort study followed patients for over 9 years and found a relative risk of 2.53 (95 % CI 1.65–3.89) in those subjects whose mean daily doses exceeded 600 μg [31]. Two recent systematic reviews also found similar dose-response relationships between inhaled glucocorticoids and fracture risk [32, 33•]. Mattishent et al. calculated the number needed to treat for harm due to fracture with IGC as 83 patients after 3 years of use [33•]. These data indicate that, as seen with oral glucocorticoids, dose and duration of treatment may be important determinants of fractures in inhaled glucocorticoid-treated individuals.

Skeletal Effects of Inhaled Glucocorticoids in Pediatric Asthmatic Patients

Asthma is the most common chronic disease of childhood. There are over 6.2 million children with asthma in the USA, and the prevalence is rising [5, 34]. Inhaled glucocorticoids are currently the first-line treatment for persistent asthma in both children and adults, with clear, demonstrated benefits to controlling asthma symptoms, improving quality of life, and reducing airway inflammation, hospitalizations, and asthma-related deaths [35]. The average age of an asthma diagnosis is 2.6 years [36]. Initiation of inhaled glucocorticoids at a young age has potential effects on bone accrual, peak bone mass, and growth in addition to the cumulative lifetime effects of these medications. Of concern are recent studies in pediatric populations, which have demonstrated detrimental effects of these medications on bone growth and density [35, 37••, 38].

A meta-analysis of 25 trials involving 8471 children with mild to moderate, persistent asthma showed that inhaled glucocorticoid treatment produced a significant mean reduction of 0.48 cm/y in linear growth velocity and a 0.61-cm deficit from baseline height after 1 year [35]. During the second year of treatment (included in five of the trials), there was no significant difference in linear growth velocity. Only two studies

measured linear growth velocity into the third year of treatment, and of these trials, one found a significantly lower growth velocity of −0.33 cm/y (95 % CI −0.52 to −0.14). The results suggest that growth suppression may be greatest within the first year of treatment and that the effect may diminish with subsequent years, although additional long-term data is needed. Of the four trials examining growth patterns after cessation of inhaled glucocorticoid treatment, three found that no significant catch-up growth occurred within 2 to 4 months after cessation. While one trial showed accelerated linear growth velocity at 12 months post-treatment, a significant difference in height remained when compared to the control group. Kelly et al. recently demonstrated that individuals who had been randomized to inhaled glucocorticoid treatment during childhood, between the ages of 5–13, had a lower mean adult height of 1.2 cm compared to individuals randomized to placebo. This effect was greatest in those individuals with high daily doses within the first 2 years of treatment [37••]. In another study, children who received regular inhaled glucocorticoid treatment before 6 years of age, had significantly reduced BMD at the lumbar spine (mean aBMD = 0.81, 95 % CI 0.74–0.90) detected by late school age (median age 12.3 years) compared to those who had never used these medications. This analysis did not find a significant impact on BMD in the children with regular IGC use between 6 and 12 years of age, suggesting that exposure before 6 years of age may have the most critical impact [38].

Although the magnitude of the difference in height is small, these results suggest that inhaled glucocorticoids significantly impact skeletal growth and bone accrual. The greatest effects appear to occur early, within the first 1 to 2 years of treatment and may be most pronounced in children who initiate treatment at early ages.

Skeletal Effects of Inhaled Glucocorticoids in Adult Asthmatic Patients

While several studies have reported lower aBMD in adult asthmatic patients using inhaled glucocorticoids compared to untreated controls [13, 21, 39–43], this finding is not uniform [44–46]. Similarly, some authors have found that asthmatic patients using inhaled glucocorticoids are at an increased risk of vertebral, hip, and other non-vertebral fractures [21, 22, 39, 45, 47], while others have not [20, 23, 28, 48, 49]. A dose-response relationship between inhaled glucocorticoids with both BMD and fracture has been reported, with a deleterious effect seen at high daily doses and larger cumulative doses in the majority of studies [22, 40, 41, 47, 50, 51]. In general, studies with mean daily dose of inhaled glucocorticoids less than 800 μg per day have not found detrimental skeletal effects of inhaled corticosteroids [48, 52]. In one of postmenopausal women, increased fractures were demonstrated even in patients using inhaled glucocorticoids who had normal BMD by DXA [18].

Several groups have investigated changes in bone turnover with inhaled glucocorticoid treatment. Studies have show an acute, rapid change in calciotropic hormones and turnover markers in the first 1–4 weeks of treatment after starting IGC treatment, with decreased bone formation and increased resorption [43, 53–56]. However, reports of the long-term effects on bone turnover are conflicting [57–60]. A recent study compared changes in bone turnover marker changes after 1 year of treatment with high (mean ciclesonide 507 μg/day) or low dose (mean ciclesonide 202 μg/day) inhaled glucocorticoid treatment for mild–moderate asthma and found no significant differences in these bone formation or resorption [58]. This study did not include a control group of asthma patients not receiving inhaled glucocorticoid treatment.

Several studies have shown an impact of inhaled glucocorticoids on bone density. In a case-control study, Monadi et al. recently investigated asthmatic patients who had been treated with inhaled glucocorticoids for an average of 6.5 years and found that patients younger than 50 years of age had significantly lower aBMD at the LS (11.3 %) and femoral neck (8.8 %) [61•]. However, there was no difference among inhaled glucocorticoid patients and healthy controls in those subjects over 50 years old. Limitations of this work are the cross sectional designs and that the controls were healthy subjects who did not have asthma. The effects of chronic illness and of glucocorticoid use during skeletal accrual could not be differentiated. There is limited longitudinal data in adult asthmatic patients. In a three year prospective study, Israel et al. demonstrated a dose-related decline in BMD at the hip in premenopausal asthmatic women using inhaled glucocorticoids [43]. In a 1-year randomized clinical trial using peripheral quantitative tomography, there were very small declines in the cortical bone in patients treated with high dose fluticasone and budesonide but no change in trabecular bone [62]. Table 1 summarizes the findings of prospective studies that have investigated changes in BMD in adult asthmatics treated with inhaled glucocorticoids.

The efficacy of various pharmacologic therapies to prevent bone loss has been investigated in asthmatic patients treated with inhaled glucocorticoids. Kasayama et al. compared treatment with a bisphosphonate (alendronate 5 mg/day) or alfacalcidol (1-α-hydroxyvitamin D3, 1 μg/day) to prevent bone loss in postmenopausal asthmatic women using long-term-inhaled glucocorticoids [63]. Women treated with alendronate for 1 year had improvements in BMD at the lumbar spine (4.9 %) and total hip (2.4 %). In women who received alfacalcidol, BMD was stable at the LS and TH. There was no untreated control group in this study, and therefore

Table 1 Prospective studies of inhaled glucocorticoids (IGC) on bone in adults with asthma

Author	Year	Sample size	Study design and population	Glucocorticoid (drug/dose)	Adjunctive treatment	Outcome
Anderson, W.J., et al.	2012	164 subjects	Adults aged 18–65 years with mild–moderate persistent asthma, randomized to different regimen of ciclesonide for 12 months	Mean ciclesonide dose 507 μg/day or 202 μg/day	None	No difference between high and low dose groups after 12 months in markers of bone formation (PINP, PIIINP) or resorption (ICTP or CTX)
Hughes, J.A., et al.	1999	59 subjects	Adult asthma patients with moderate to severe asthma, randomized to inhaled fluticasone propionate or inhaled budesonide for 12 months	Inhaled fluticasone propionate group 500 μg BID; inhaled budesonide 800 μg BID	None	No evidence of decrease in BMD at the spine, femoral neck, or trochanter
Israel, E., et al.	2001	109 subjects	Premenopausal women aged 18–45 with asthma followed for 3 years	Inhaled triamcinolone acetonide (≥400 μg/day)	None	IGC associated with dose-related decline in bone density at the total hip and trochanter. No dose-related effect at the femoral neck or spine.
Kasayama, S., et al.	2005	28 subjects	Postmenopausal women with asthma on IGC, randomized to treatment with alendronate or alfacalcidol for 12 months	Mean IGC dose in alendronate group 428 μg/day; mean IGC dose in alfacalcidol group 570 μg/day	Alendronate 5 mg/day or alfacalcidol 1 μg/day	BMD increased significantly at the lumbar spine, total hip, and Ward's triangle in alendronate group after 12 months. There was no significant change in alfacalcidol group
Maspero, J., et al.	2013	566 subjects	Adult patients with at least a 3-month history of asthma and no IGC use within the previous 3 months, randomized to varying IGC treatment regimen or non-steroid treatment for 12 months	Mometasone furoate 200 or 400 μg/day; fluticasone propionate 250 μg BID; montelukast sodium 10 mg/day	Calcium and vitamin D supplements	No significant decrease in the lumbar BMD in any group. Slight decrease at FN, significantly greater with fluticasone vs low dose mometasone
McDonald, C.F., et al.	2006	108 subjects	Men and women aged 20–70 with moderate to severe asthma using IGCs randomized to calcitriol or placebo for 24 months	≥800 μg/day of beclomethasone dipropionate or equivalent maintenance therapy	Oral calcitriol 0.25 μg BID or placebo	Bone loss (BMD) at the femoral neck in both groups and at the lumbar spine in group treated with calcitriol after 24 months using DXA. Calcitriol treatment did not prevent bone loss at either site.
Medici, T.C., et al.	2000	69 subjects	Adults with mild to moderate asthma, randomized to varying regimen of fluticasone propionate and beclomethasone dipropionate for 12 months	Fluticasone propionate (400 μg/day or 750 μg/day), beclomethasone dipropionate (800 μg/day or 1500 μg/day)	None	No loss of trabecular bone in the distal radius or tibia by peripheral quantitative computed tomography (pQCT) in any treatment arm over 12 months
Tattersfield, A.E., et al.	2001	239 subjects	Adults with mild asthma, randomized to inhaled budesonide, inhaled beclomethasone dipropionate, or non-steroid treatment for 2 years	Mean dose in inhaled budesonide group 389 μg/day; mean dose in inhaled beclomethasone group 499 μg/day	None	No significant difference in BMD at the lumbar spine or the femoral neck between IGC-treated asthmatics and non-IGC-treated asthmatic control group

whether significant bone loss would have occurred in the absence of treatment cannot be determined. In a recent study, BMD was followed over 1 year in asthmatic patients randomized to one of three inhaled glucocorticoid regimen: mometasone furoate 200 or 400 μg/day, fluticasone propionate 500 μg/day, or to non-steroidal treatment with montelukast sodium (10 mg/day). All subjects received calcium and vitamin D. There were no significant declines in BMD at the spine, hip, or femoral neck in any group [64•]. Further prospective research is needed to identify those patients at greatest risk for bone loss as well as the efficacy of different treatment regimen to prevent bone loss.

Skeletal Effects of Inhaled Glucocorticoids in COPD Patients

Patients with COPD are at a high risk for osteoporosis and fractures. The prevalence of osteoporosis in patients with COPD is estimated to be between 4 and 59 % and of vertebral compression fractures, between 24 and 63 % [65]. In contrast with asthmatic patients, only individuals with severe COPD are treated with chronic inhaled glucocorticoids. Research on the effects of inhaled glucocorticoids on bone in the COPD population has been inconclusive. This may relate to an inability to differentiate the detrimental skeletal effects of the medications from those of COPD itself. The independent adverse effects of COPD on the skeleton are multifactorial and relate to chronic activation of inflammatory cytokines, hypoxemia, and other factors [25, 26, 66, 67]. In COPD patients who have not had significant exposure to oral glucocorticoids, there is evidence of disrupted microarchitecture with lower cancellous bone volume, lower trabecular and trabecular thickness, lower cortical width and connectivity density, and higher trabecular separation and cortical porosity [66]. Two systematic reviews in patients with COPD have found no increased risk of fractures in inhaled glucocorticoid users compared to non-users [68, 69]. Calverley et al. conducted a large double-blind trial of 6112 COPD patients assigned to low dose inhaled glucocorticoids or placebo and after 3 years of follow-up, there was no significant difference in fracture incidence between the groups, however, this study was designed to investigate survival as the primary outcome and not skeletal events [70]. A record linkage study of 3243 COPD patients exposed to IGCs showed no association with fracture hospitalization [71•]. The study utilized health informatics records of a population of over 400,000 people in Tayside, Scottland to investigate an association between COPD patients with an existing IGC prescription and an ICD10 code for a hospitalization for fractures. All fracture types were included. This study was not able to capture the potential effects of systemic glucocorticoid use in its population. By using fractures that led to hospitalization as an endpoint, the results did not capture asymptomatic vertebral fractures or many fractures that did not result in admission. Furthermore, adherence to prescribed IGCs was not known, only that subjects had received a prescription.

Effects on bone density in patients with COPD may be dose-dependent, as seen in asthmatics. Treatment duration may also play a role. In contrast to the above studies, a systematic review by Loke et al. did find an increased risk of fracture in COPD patients and a dose-response relationship such that each 500 μg increase in beclomethasone equivalents was associated with a 9 % increased risk of fractures [72]. The Lung Health Study Research Group observed patients receiving daily dose of 1200 μg of triamcinolone acetonide, while there was no effect on BMD after 1 year of use, significant declines at the LS and FN were observed after 3 years [73]. Similarly, Scanlon et al. randomized patients with mild to moderate COPD to 1200 μg of triamcinolone acetonide or placebo for 3 years. Both groups had declines in BMD at the femoral neck, but losses were significantly greater among inhaled glucocorticoid-treated subjects [74].

In contrast, a four-year randomized clinical trial of male COPD subjects treated with low dose inhaled budesonide or long-acting β2 agonists and anticholinergics failed to find an effect on BMD. Compared to healthy controls, all patients with COPD had significantly lower BMD at baseline and a greater bone loss over 4 years. In a sub-group analysis, subjects were analyzed according to predominant underlying disease characteristics (bronchitic or emphysematic). Patients with predominantly emphysematic disease showed comparable bone loss with both treatments. Surprisingly, patients with bronchitic disease treated with inhaled glucocortioids had less bone loss at the hip compared to bronchitic patients treated with β2 agonists and anticholinergics [75]. The authors hypothesize that lower rates of bone loss seen in the IGC group may have been related to reduced systemic inflammation; however, inflammatory markers were not measured in this study so that effect could not be conclusively determined. Table 2 summarizes the findings of prospective studies investigating the effects of inhaled glucocorticoids on bone in COPD patients.

In a small study, evaluating histomorphometry in postmenopausal women with COPD microarchitectural parameters and remodeling indices were worse compared to historical controls [66]. However, the only difference between women with COPD who were and were not treated with inhaled glucocorticoids was lower mineralized surface in treated women. Of note, 30 % of IGC users in this study also used oral glucocorticoids for disease flare-ups with an average cumulative dose of ~400 mg. A follow-up study on this cohort evaluated bone mineral density distribution (BMDD), a contributor to the elasticity and stiffness of bone, and therefore strength and

Table 2 Prospective studies of inhaled glucocorticoids (IGC) on bone in adults with COPD

Author	Year	Sample size	Study design and population	Glucocorticoid (drug/dose)	Adjunctive treatment	Outcome
Calverley, P.M., et al.	2007	6112 subjects	Adults aged 40–80 with COPD, randomized to varying IGC regimen or placebo for 3 years	Combination salmeterol 50 μg/day and fluticasone propionate 500 μg/day; salmeterol 50 μg/day alone; fluticasone propionate 500 μg/day alone; placebo	None	Primary outcome: survival. No significant difference in clinical fracture (secondary outcome)
Lung Health Study Research Group	2000	1116 subjects	Adults with COPD, randomized to IGC or placebo for 3 years	Inhaled triamcinolone acetonide 600 μg BID or placebo	None	No significant difference between groups at 1 year. At 3 years, IGC group had greater bone loss at the lumbar spine and femur
Mathioudakis, A.G. et al.	2013	564 subjects	Men with COPD (251) and controls (313). COPD patients were randomized to beta agonists and anticholinergics with or without IGC	Budesonide 320 μg/day or placebo	None	Similar hip bone loss in subjects treated with/without IGC with underlying emphysema. Less bone loss at the hip in IGC-treated subjects with underlying bronchitic disease
Scanlon, P.D., et al.	2004	412 subjects	Adults with mild to moderate chronic obstructive pulmonary disease	Triamcinolone acetonide 600 μg BID or placebo	None	After 3 years, IGC-treated subjects had significantly lower BMD at the femoral neck and lumbar spine compared to placebo. More participants in IGC-treated group had high rates of loss (≥6 %) at the femoral neck

susceptibility to fracture. BMDD was not different between COPD patients and controls, and the authors again found no effect of inhaled glucocorticoids [76]. Given the small sample size, it is not possible whether the lack of an effect may have been related to inadequate power in this study.

Conclusions

The literature offers conflicting evidence on whether and to what extent inhaled glucocorticoids have detrimental skeletal effects. Differences in characteristics of the study populations, including sex, age, menopausal status, underlying pulmonary disease, and disease severity, as well as co-morbidities all contribute to the heterogeneity of results. Importantly, dose and duration of inhaled glucocorticoid therapy vary markedly by study. Recent studies have shown that inhaled glucocorticoid treatment for pediatric asthma has significant effects on immediate growth velocity, childhood bone density, and adult height. The effects occur primarily within the first 2 years of treatment and are greatest when these medications are initiated before the age of six. Prospective studies have demonstrated bone loss after initiation of inhaled glucocorticoids in premenopausal women with asthma. There is a dose-response relationship between inhaled glucocorticoids and fracture risk. The majority of studies of vertebral and non-vertebral fractures show an increased risk in those subjects treated with the highest doses. Duration of inhaled glucocorticoid use may be associated with declines in BMD. While patients with COPD have lower BMD and higher fracture rates compared to controls, the majority of studies have not found an additional detrimental effect of inhaled glucocorticoids on bone. It may be that the skeletal effects of the disease itself eclipse those of the medication, particularly in low and moderate doses of inhaled glucocorticoids. Given the amount of contradictions in the literature, it is not possible at present to make definitive conclusions about the skeletal effects of inhaled glucocorticoids. However, the evidence from many studies of a dose-response relationship with fracture supports clinical management strategies using the lowest possible dose of inhaled glucocorticoids for the patients with asthma and COPD. Considering the lack of consensus as to how patients on IGC should be evaluated or treated for their skeletal health, and the increasing number of patients using chronic IGCs, further research into this topic is critical.

Compliance with Ethical Standards

Conflict of Interest Stephanie A. Sutter and Emily M. Stein declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Diaz-Guzman E, Mannino DM. Epidemiology and prevalence of chronic obstructive pulmonary disease. Clin Chest Med. 2014;35(1):7–16.
2. Jemal A et al. Trends in the leading causes of death in the United States, 1970-2002. JAMA. 2005;294(10):1255–9.
3. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet. 2012;379(9823):1341–51.
4. Croisant S. Epidemiology of asthma: prevalence and burden of disease. Adv Exp Med Biol. 2014;795:17–29.
5. CDC. National surveillance for asthma—United States, 1980-2004. MMWR. 2007;56:1–14; 18-54.
6. CDC's Behavioral Risk Factor Surveillance System. Available from: http://www.cdc.gov/brfss/acbs/2010/prevalence_tables/table9.html.
7. National Heart, Lung, and Blood Institute. Asthma: Frequently Asked Questions. Available at: http://www.nhlbi.nih.gov/health-pro/resources/lung/asthma-data-surveillance/faq.
8. Yawn BP et al. Inhaled corticosteroid use in patients with chronic obstructive pulmonary disease and the risk of pneumonia: a retrospective claims data analysis. Int J Chron Obstruct Pulmon Dis. 2013;8:295–304.
9. Weinstein RS et al. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. J Clin Invest. 1998;102(2):274–82.
10. Ohnaka K et al. Glucocorticoid suppresses the canonical Wnt signal in cultured human osteoblasts. Biochem Biophys Res Commun. 2005;329(1):177–81.
11. Sambrook PN. Anabolic therapy in glucocorticoid-induced osteoporosis. N Engl J Med. 2007;357(20):2084–6.
12. Vanderoost J et al. Glucocorticoid-induced changes in the geometry of osteoclast resorption cavities affect trabecular bone stiffness. Calcif Tissue Int. 2013;92(3):240–50.
13. Compston J. Clinical question: What is the best approach to managing glucocorticoid-induced osteoporosis? Clin Endocrinol (Oxf). 2011;74(5):547–50.
14. van Staa TP et al. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology (Oxford). 2000;39(12):1383–9.
15. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int. 2002;13(10):777–87.
16. Van Staa TP et al. Use of oral corticosteroids and risk of fractures. J Bone Miner Res. 2000;15(6):993–1000.
17. Van Staa TP et al. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum. 2003;48(11):3224–9.
18. Sutter S et al. Abnormalities in cortical bone, trabecular plates, and stiffness in postmenopausal women treated with glucocorticoids. J Clin Endocrinol Metab. 2014;99(11):4231–40.
19. Johnson M. Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids. J Allergy Clin Immunol. 1996;97(1 Pt 2):169–76.
20. de Vries F et al. Use of inhaled and oral glucocorticoids, severity of inflammatory disease and risk of hip/femur fracture: a population-based case-control study. J Intern Med. 2007;261(2):170–7.
21. Richy F et al. Inhaled corticosteroids effects on bone in asthmatic and COPD patients: a quantitative systematic review. Osteoporos Int. 2003;14(3):179–90.
22. Vestergaard P et al. Corticosteroid use and risk of hip fracture: a population-based case-control study in Denmark. J Intern Med. 2003;254(5):486–93.
23. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk in patients with chronic lung diseases treated with bronchodilator drugs and inhaled and oral corticosteroids. Chest. 2007;132(5):1599–607.
24. Campbell IA et al. Five year study of etidronate and/or calcium as prevention and treatment for osteoporosis and fractures in patients with asthma receiving long term oral and/or inhaled glucocorticoids. Thorax. 2004;59(9):761–8.
25. Jorgensen NR et al. The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease: a cross sectional study. Respir Med. 2007;101(1):177–85.
26. Nuti R et al. Vertebral fractures in patients with chronic obstructive pulmonary disease: the EOLO Study. Osteoporos Int. 2009;20(6):989–98.
27. Cochrane MG et al. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. Chest. 2000;117(2):542–50.
28. Jones A, et al. Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. Cochrane Database Syst Rev, 2002(1): p. Cd003537.
29. Suissa S et al. Inhaled and nasal corticosteroid use and the risk of fracture. Am J Respir Crit Care Med. 2004;169(1):83–8.
30. Hubbard RB et al. Inhaled corticosteroids and hip fracture: a population-based case-control study. Am J Respir Crit Care Med. 2002;166(12 Pt 1):1563–6.
31. Hubbard R et al. Use of inhaled corticosteroids and the risk of fracture. Chest. 2006;130(4):1082–8.
32. Etminan M et al. Inhaled corticosteroids and the risk of fractures in older adults: a systematic review and meta-analysis. Drug Saf. 2008;31(5):409–14.
33.• Mattishent K et al. Meta-review: adverse effects of inhaled corticosteroids relevant to older patients. Drugs. 2014;74(5):539–47. **This meta-review included five meta-analyses and 3 additional articles. The authors found a dose response relationship between IGC dose and the risk of fracture in older patients with asthma and COPD**.
34. CDC. Disabilities among children aged ≤ 17 years—United States, 1991-1992. MMWR. 1995;44:609–13.
35. Zhang L, Prietsch SO, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: effects on growth. Evid Based Child Health. 2014;9(4):829–930.
36. Radhakrishnan DK et al. Trends in the age of diagnosis of childhood asthma. J Allergy Clin Immunol. 2014;134(5):1057–62.e5.
37.•• Kelly HW et al. Effect of inhaled glucocorticoids in childhood on adult height. N Engl J Med. 2012;367(10):904–12. **Prospective study in children with asthma who were randomized to treatment with inhaled glucocorticoids, nedocromil, or placebo. Mean adult height was lower in the group treated with inhaled glucocorticoids, and the effect was greatest for patients who received the largest doses in the first two years of treatment**.
38. Sidoroff VH et al. Inhaled corticosteroids and bone mineral density at school age: a follow-up study after early childhood wheezing. Pediatr Pulmonol. 2015;50(1):1–7.
39. Dam TT et al. Bone mineral density and fractures in older men with chronic obstructive pulmonary disease or asthma. Osteoporos Int. 2010;21(8):1341–9.
40. Wong CA et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. Lancet. 2000;355(9213):1399–403.
41. Jung JW et al. Are asthmatic patients prone to bone loss? Ann Allergy Asthma Immunol. 2014;112(5):426–31.

42. McDonald CF, Zebaze RM, Seeman E. Calcitriol does not prevent bone loss in patients with asthma receiving corticosteroid therapy: a double-blind placebo-controlled trial. Osteoporos Int. 2006;17(10): 1546–51.
43. Israel E et al. Effects of inhaled glucocorticoids on bone density in premenopausal women. N Engl J Med. 2001;345(13):941–7.
44. Elmstahl S et al. Is there an association between inhaled corticosteroids and bone density in postmenopausal women? J Allergy Clin Immunol. 2003;111(1):91–6.
45. Sosa M et al. Inhaled steroids do not decrease bone mineral density but increase risk of fractures: data from the GIUMO Study Group. J Clin Densitom. 2006;9(2):154–8.
46. Kuan YC et al. Bone mineral density in asthmatic patients on inhaled corticosteroids in a developing country. Ann Thorac Med. 2012;7(2):69–73.
47. Weatherall M et al. Dose-response relationship for risk of non-vertebral fracture with inhaled corticosteroids. Clin Exp Allergy. 2008;38(9):1451–8.
48. Tattersfield AE et al. Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. Thorax. 2001;56(4): 272–8.
49. Hughes JA et al. One year prospective open study of the effect of high dose inhaled steroids, fluticasone propionate, and budesonide on bone markers and bone mineral density. Thorax. 1999;54(3): 223–9.
50. van Staa TP, Leufkens HG, Cooper C. Use of inhaled corticosteroids and risk of fractures. J Bone Miner Res. 2001;16(3):581–8.
51. Ip M et al. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. Chest. 1994;105(6):1722–7.
52. Matsumoto H et al. Effects of inhaled corticosteroid and short courses of oral corticosteroids on bone mineral density in asthmatic patients : a 4-year longitudinal study. Chest. 2001;120(5):1468–73.
53. Hodsman AB et al. Differential effects of inhaled budesonide and oral prednisolone on serum osteocalcin. J Clin Endocrinol Metab. 1991;72(3):530–40.
54. Puolijoki H et al. Inhaled beclomethasone decreases serum osteocalcin in postmenopausal asthmatic women. Bone. 1992;13(4):285–8.
55. Toogood JH et al. Effects of dose and dosing schedule of inhaled budesonide on bone turnover. J Allergy Clin Immunol. 1991;88(4): 572–80.
56. Ali NJ, Capewell S, Ward MJ. Bone turnover during high dose inhaled corticosteroid treatment. Thorax. 1991;46(3):160–4.
57. Fujita K et al. Inhaled corticosteroids reduce bone mineral density in early postmenopausal but not premenopausal asthmatic women. J Bone Miner Res. 2001;16(4):782–7.
58. Anderson WJ, McFarlane LC, Lipworth BJ. Prospective follow-up of novel markers of bone turnover in persistent asthmatics exposed to low and high doses of inhaled ciclesonide over 12 months. J Clin Endocrinol Metab. 2012;97(6):1929–36.
59. Kerstjens HA et al. Effects of short-term and long-term treatment with inhaled corticosteroids on bone metabolism in patients with airways obstruction. Dutch CNSLD Study Group. Thorax. 1994;49(7):652–6.
60. Li JT et al. Fluticasone propionate powder and lack of clinically significant effects on hypothalamic-pituitary-adrenal axis and bone mineral density over 2 years in adults with mild asthma. J Allergy Clin Immunol. 1999;103(6):1062–8.
61.• Monadi M et al. Impact of treatment with inhaled corticosteroids on bone mineral density of patients with asthma: related with age. Osteoporos Int. 2015;26(7):2013–8. **Case control study compared bone density in asthmatic patients treated with long-term inhaled glucocorticoids and healthy controls. An effect of treatment was observed in patients younger than 50 but not in older patients**.
62. Medici TC et al. Effect of one year treatment with inhaled fluticasone propionate or beclomethasone dipropionate on bone density and bone metabolism: a randomised parallel group study in adult asthmatic subjects. Thorax. 2000;55(5):375–82.
63. Kasayama S et al. Effects of alendronate on bone mineral density and bone metabolic markers in postmenopausal asthmatic women treated with inhaled corticosteroids. Metabolism. 2005;54(1):85–90.
64.• Maspero J et al. Effects of mometasone, fluticasone, and montelukast on bone mineral density in adults with asthma. J Allergy Clin Immunol Pract. 2013;1(6):649–55.e1. **This randomized double-blind clinical trial investigated the effects of different asthma regimen on areal bone mineral density. There were no significant declines in BMD at the spine or total hip over one year in subjects treated with mometasone, fluticasone or monteleukast**.
65. Lehouck A et al. COPD, bone metabolism, and osteoporosis. Chest. 2011;139(3):648–57.
66. Kulak CA et al. Skeletal microstructural abnormalities in postmenopausal women with chronic obstructive pulmonary disease. J Bone Miner Res. 2010;25(9):1931–40.
67. Tantucci C. COPD and osteoporosis: something more than a comorbidity. Endocrine. 2012;42(1):5–6.
68. Yang IA, et al. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012;**7**: p. Cd002991.
69. Drummond MB et al. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA. 2008;300(20):2407–16.
70. Calverley PM et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775–89.
71.• Flynn RW et al. Quantifying the real life risk profile of inhaled corticosteroids in COPD by record linkage analysis. Respir Res. 2014;15:141. **Record linkage study linking COPD datasets with prescription and hospitalization data. Use of inhaled glucocorticoids was not associated with hospitalization for fractures. Only clinical (not radiographic) and fractures severe enough to warrant hospitalization were included**.
72. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax. 2011;66(8):699–708.
73. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med. 2000;343(26):1902-9.
74. Scanlon PD et al. Loss of bone density with inhaled triamcinolone in Lung Health Study II. Am J Respir Crit Care Med. 2004;170(12): 1302–9.
75. Mathioudakis AG et al. Impact of long-term treatment with low-dose inhaled corticosteroids on the bone mineral density of chronic obstructive pulmonary disease patients: aggravating or beneficial? Respirology. 2013;18(1):147–53.
76. Misof BM et al. Subtle changes in bone mineralization density distribution in most severely affected patients with chronic obstructive pulmonary disease. Bone. 2015;79:1–7.