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Long-term therapy in COPD: any evidence of adverse effect on bone?

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Abstract: Patients with COPD have high risk for osteoporosis and fractures. Hip and vertebral fractures might impair mobility, and vertebral fractures further reduce lung function. This review discusses the evidence of bone loss due to medical treatment opposed to disease severity and risk factors for COPD, and therapeutic options for the prevention and treatment of osteoporosis in these patients. A review of the English-language literature was conducted using the MEDLINE database until June 2009. Currently used bronchodilators probably lack adverse effect on bone. Oral corticosteroids (OCS) increase bone resorption and decrease bone formation in a dose response relationship, but the fracture risk is increased more than reflected by bone densitometry. Inhaled corticosteroids (ICS) have been associated with both increased bone loss and fracture risk. This might be a result of confounding by disease severity, but high doses of ICS have similar effects as equipotent doses of OCS. The life-style factors should be modified, use of regular OCS avoided and use of ICS restricted to those with evidenced effect and probably kept at moderate doses. The health care should actively reveal risk factors, include bone densitometry in fracture risk evaluation, and give adequate prevention and treatment for osteoporosis.

Keywords: COPD, corticosteroids, bronchodilators, bone mineral density, osteoporosis, fractures

Introduction

Chronic obstructive pulmonary disease (COPD) is, and will increasingly be, a major cause of morbidity and mortality worldwide.¹ COPD develops as a consequence of genetic susceptibility, increasing life span, environment and life-style factors. Aging of the population, shared risk factors, especially tobacco smoking, systemic effects by the disease and side effects of treatment contribute to the fact that COPD patients often have many co-morbidities.²⁻⁴ among these osteoporosis and increased fracture risk.

Patients with moderate to severe COPD have limitations in physical activity, and fractures inevitably could be a heavy additional burden to their dyspnea. Among the oldest, the often disabling consequences of hip fractures frequently initiate the patients' need for home care, transfer to nursery homes and shortening of life. Vertebral fractures influence the mobility of the patients, are associated with back pain, and may also increase dyspnea, as increased thoracic kyphosis and decreased rib mobility add a restrictive component to their lung disease.^{5,6} Hence, effort should be given to secure as good "bone health" as possible in this group of patients.

The aims of this paper are to discuss the potential and observed adverse effect on bone by the medical treatment given to COPD patients, and also discuss to some extent,

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the contribution by the disease itself, life-style factors and co-morbidities. Further, preventive and treatment strategies for osteoporosis are discussed.

Methods

A MEDLINE literature search for English language papers published until June 2009 was conducted using relevant key terms, in addition to examination of reference lists from pivotal studies and reviews.

Medical treatment of COPD

According to the Global initiative for chronic Obstructive Lung Disease's guidelines (GOLD), www.goldcopd.com, bronchodilator medications are the main symptomatic treatment of COPD and these include short and long-acting β_2 -agonists and anticholinergics. They increase exercise capacity and health status, whilst long-acting anticholinergics additionally reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. Theophylline also is effective in COPD, but due to its potential toxicity inhaled bronchodilators are preferred.¹

Inhaled corticosteroids (ICS) are recommended for severe COPD patients with repeated exacerbations, as they have been shown to reduce the frequency of exacerbations and thus improve health status. ICS combined with a long-acting β_2 -agonist (LABA) are more effective than the individual components.¹ A recent network meta-analysis by Puhan and coworkers concluded that for mild to moderate COPD, single treatment with LABA or long-acting anticholinergics was the treatment of choice both for symptom control and exacerbation prevention, but for those with $FEV_1 < 40\%$ predicted, long-acting anticholinergics was as effective as combination treatment in reducing exacerbations.⁷

Oral corticosteroids (OCS) are recommended for 7 to 10 days with 30 to 40 mg prednisolone in exacerbations in patients with severe COPD, but chronic treatment with OCS should be avoided.¹

Osteoporosis

Bone

The skeleton is essential for terrestrial animal life, and human beings have evolved bone light enough to enable rapid mobility and strong enough to avoid disabling fractures during reproductive life.⁸

Bone mass reaches the peak at age 25 to 30 years.⁹ After a plateau phase, bone loss occurs throughout life with an age-associated annual bone loss of approximately 0.5% to 1%, but the rate of loss differs by sex, skeletal sites and age.

In men, there is a rather constant bone loss from age 25 to 39 years, this increases mainly at the hips at age ≥ 65 years,¹⁰ with further loss of cortical bone above the age of 75 years.¹¹ In women, bone loss begins at age 40 to 44, and is particularly rapid in the total hip at age 50 to 54 with a change of -6.8% over 5 years, with another acceleration in loss after age of 70 years.^{10,11}

Prevalence of osteoporosis

Osteoporosis is the main risk factor for fragility fractures, defined as a fracture occurring after a fall from standing height or minor trauma. The lifetime risk of any fracture at age 50 years is about 50% among women and 20% among men.¹² Men at age 75 years have equivalent fracture risk as women aged 65 years.¹³

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk for fracture. Bone strength primarily reflects the integration of bone density and bone quality.¹⁴ An operational definition of osteoporosis, established by The World Health Organization (WHO), is based on bone mineral density (BMD).¹⁵ Bone densitometry results are given as area density, but also as T-scores (standard deviations [SD] compared with young adult sex-matched controls) and Z-scores (compared with age- and sex matched controls). The WHO has defined osteopenia as BMD T-score -1 to -2.5 SD and osteoporosis as T-score below -2.5 SD.¹⁵

Measures of BMD, bone quality and bone metabolism

Dual energy absorptiometry (DXA) at the hip is the best predictor of hip fractures and best standardized for the diagnosis of osteoporosis. Spine and hip BMD have similar value for predicting spine fractures,¹⁶ but spondylarthrosis and minerals in the aorta might give artificially high values of BMD in the anterior-posterior directed measurements after the age of 60 to 65.¹⁷

BMD at these sites are widely used in clinical practice to identify those at increased risk for fracture. However, a majority of fragility fractures occurs in women not being defined as osteoporotic.¹⁸ The prediction of fractures in both genders improves if baseline BMD is replaced with change in BMD between measurements in the models.¹⁹ Most clinicians, however, have to rely on one measurement estimating the patients fracture risk. Compared to other risk factors, BMD is at least as good in prediction of fracture as blood pressure measurements to predict stroke and level of cholesterol to predict cardiac infarction.²⁰

T-scores between different sites should not be compared, due to site differences regarding accuracy errors, variance in the population and algorithms for edge detections.²¹ In a study of the same population of a DTX-base, the prevalence of osteoporosis in women aged 50 years or more, ranged from 11% at the hip, 24% at the spine, to 52% at the distal radius.²²

Mainly for research purposes, methods like Single X-ray Absorptiometry (SXA), Quantitative Ultrasound (QUS) and Quantitative Computed Tomography (QCT) have been used. Although measurement at a specific site is the best predictor of fracture at that site, forearm SXA is as good as lumbar BMD for prediction of hip fracture,^{23,24} other non-spine fractures²⁵ and fragility fractures in general.²⁶ Correspondingly, quantitative ultrasound (QUS) of calcaneus has been used to estimate regional BMD-levels, evaluate bone quality²⁷ and predict fracture risk,^{28,29} but this method has poor sensitivity for detecting osteoporosis defined as T-score < -2.5 SD.³⁰

Markers of bone turnover, as alkaline phosphatase, hydroxyproline, osteocalcin, pro-collagen peptides and pyridinium crosslinks, can enhance the predictive value of BMD.²⁰ However, due to large biological variability, they are of uncertain clinical relevance and have not been shown

to predict the risk of fracture^{31,32} or to correlate with changes in BMD.³³ They might, however, reflect changes related to antiresorptive therapy more rapidly than changes in BMD.³⁴ In general, corticosteroid (CS) administration is followed by a reduction in bone formation markers, especially serum osteocalcin levels,³⁵⁻³⁷ and a trend to an increase or no change in bone resorption markers.³⁸

Risk factors for osteoporosis and fracture in COPD

High age and female sex are important risk factors for osteoporosis, with postmenopausal loss of ovarian hormones being the single most important factor. The prevalence of osteoporosis and incidence of fragility fractures differ substantially between populations, with highest figures in post-menopausal women of Northern European descent, especially those living in Scandinavia.^{12,39-41} Both parental osteoporosis and fragility fractures, as well as previous fracture in the patient, are risk factors for further fracture.⁴²

Patients with COPD are at high risk for osteoporosis and fractures because of lifestyle factors, systemic effects of the disease, treatment and comorbidities (Figure 1). Smoking is associated with low BMD in a dose-response relationship,

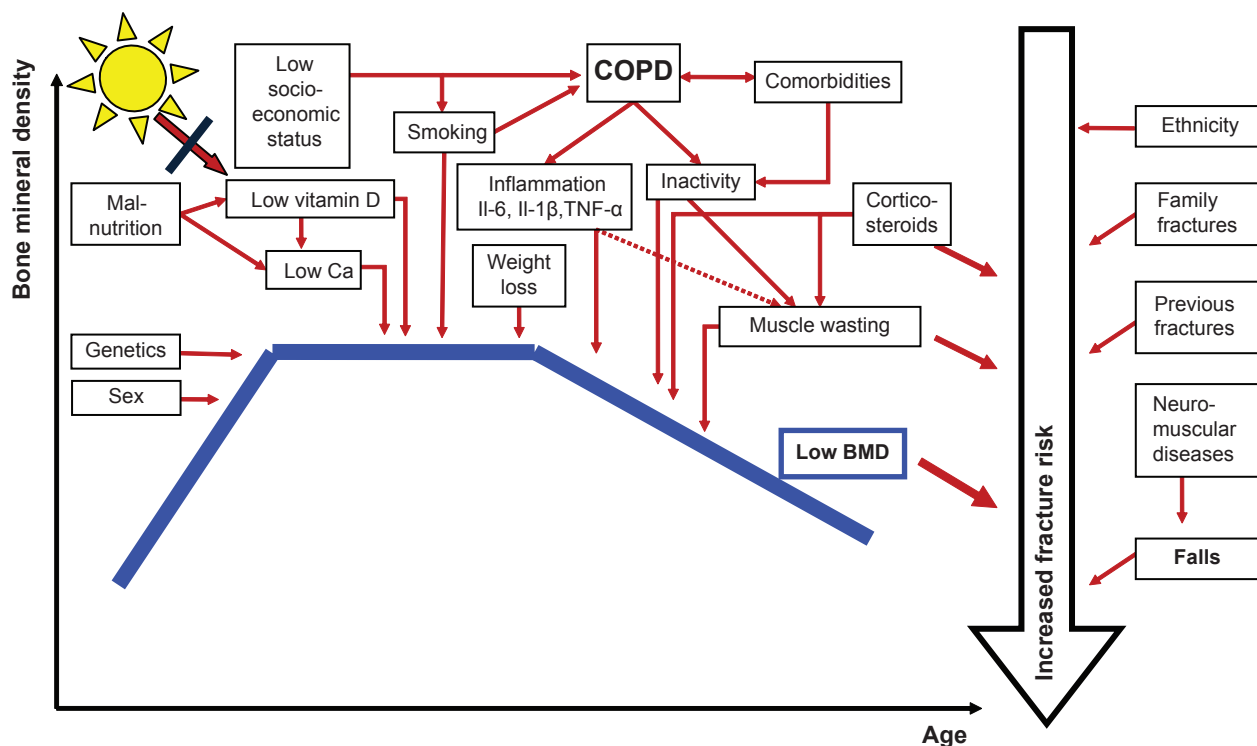


Figure 1 The development of bone mineral density (BMD) throughout life, factors of importance for level of BMD (genetics, sex), COPD-related factors lowering (BMD), and important factors influencing fracture risk in addition to level of BMD.

Abbreviations: IL, interleukin; TNF- α , tumor necrosis factor alpha.

not only in current smokers, but even ex-smokers.^{43,44} Female lungs seem to be more susceptible to harmful effects of tobacco smoking than male lungs.^{45,46} Increased prevalence of smoke related lung diseases in women and increasing proportion of women among smokers, might affect bone more negatively in women than men, through combined effects of COPD and smoking.

Furthermore, inactivity is an important risk factor for osteoporosis and fractures, partly due to increased risk for falling. A physically active life has been found to nearly halve the incidence of hip fractures in the older population,⁴⁷ and appendicular lean mass accounts for most of the explained variance among factors being positively associated with BMD.⁴¹

COPD patients, as well as patients with other chronic diseases, often have deficient calcium (Ca) and vitamin D nutritional status,^{48,49} and the latter is frequently accentuated because of little exposure to sunlight. Weight loss is also associated with decreased BMD^{50–52} and a recent review reported BMD to be 3% to 7% higher for every 10 kg increase in weight.⁴³ Correspondingly, a recent study found that $\geq 5\%$ weight loss was associated with a 33% increased risk of forearm fractures.⁵³

In the recent years, a detrimental effect on bone also caused by COPD itself has been suggested.^{3,54} Among many possible explanations, most current evidence indicates that this is a result of mediators, cytokines (interleukin [IL]-6, IL-1 β and TNF- α) or activated inflammatory cells reaching the systemic circulation from inflammation in the lungs.^{3,4} The extent of this contribution is unclear, but the fact that patients on OCS have higher risk of fractures compared to untreated patients with similar underlying inflammatory diseases⁵⁵ indicates that this is not one of the main causes of the influence on bone.

Medicine-induced osteoporosis in COPD

Many studies have addressed this subject, but the main problem or limitation of many of these studies are the power to reveal any effect, and, in case of effect, to differentiate between possible effects by medication, disease severity and factors mentioned above. There have been a few large, randomized, double-blind, clinical trials (RCT), many observational case-control and cohort studies, in addition to many meta-analyses. Some larger and important studies are based on registers as the UK General Practice Research Database (GPRD) (190,000 to 240,000 cases using CS).^{56,57} and Danish data based on the National Hospital Discharge Register and others ($>125,000$ fracture cases).⁵⁸

How can adverse effects on bone be measured?

Outcomes such as fractures, or surrogate measures of fracture risk, as BMD and biochemical markers for bone turnover, might be relevant for studies on adverse effects on bone. RCT including fractures as primary outcome would give the best evidence of such an effect. However, even as lifetime fracture risk is high, only a small number of subjects at risk actually sustain a fracture during few years observation time. For example, in any year, fractures occur in 1 to 2 per 100 women aged 65 years, 6 to 10 per 100 women aged 75 years, and only 1 to 2 per 2,000 of the 15% of women <60 years of age with osteoporosis.⁵⁹ Even for BMD, there are problems with the power of studies. Wisniewski et al calculated that a prospective study comparing a dose of 1 mg beclomethasone dipropionate (BDP) equivalents with placebo, would require 2,500 individuals in each limb for 95% power to detect the difference of 0.1 SD in BMD found in their cross-sectional study.⁶⁰

Airway obstruction, COPD and bone

Airflow obstruction is associated with increased risk of osteoporosis compared with normal lung function.^{61,62} COPD is an independent predictor of BMD reduction^{63–65} and vertebral fracture risk.⁶⁶ Studies have shown more than two-fold prevalence of osteoporosis in CS-naïve COPD patients, compared both with healthy controls⁶⁷ and asthma patients.⁶⁸ Increasing disease severity increases the risk for osteoporosis,^{29,61,69} and in severe COPD osteoporosis and osteopenia have been found in as many as 66% and 31%, respectively.⁷⁰

Correspondingly, the fracture risk is positively associated with COPD severity.⁷¹ In mild COPD the fracture risk is similar to what was found in the European Vertebral Osteoporosis Study (EVOS),⁷² with a prevalence of vertebral deformity of 12% in both genders aged 50 to 79 years,⁷³ but more COPD patients than healthy, had at least 1 severe vertebral fracture (OR = 3.75).⁶ Nuti et al reported at least 1 vertebral fractures in about 40% of COPD patients, with a strong association between disease severity and fractures, especially in men,⁷¹ and in a recent Norwegian study, the number of vertebral deformities was almost twice as high in GOLD stage III compared to II in women.⁷⁴ In the large Danish register study, comparing subjects with and without COPD, COPD adjusted for use of CS was associated with increased risk for hip and vertebral fracture (relative risk [RR] 1.63 and 1.23), but not for forearm fractures. Comparing those with and without asthma, revealed an asthma-related increased risk for only hip fracture (RR 1.32).⁵⁸

Vertebral compression fractures often are asymptomatic, and among severe COPD patients, not previously diagnosed compression fractures were found in 24%.⁷⁵ A prospective study revealed that compared to subjects without COPD, incident COPD patients had increased risk for osteoporosis and fracture (RR 3.1 and 1.6, respectively) within the first year after diagnosis.²

Treatment of COPD and effect on bone

Oral glucocorticoids

A GPRD study documented that women aged ≥ 85 years using ≥ 7.5 mg prednisolone daily had an excess in number of hip fracture cases of 1.4 cases per 100 patients per year compared to non-users, and as many as 47% and 72% of all hip and vertebral fractures, respectively, could be attributed to OCS.⁷⁶ Walsh et al found that patients on OCS for ≥ 6 months compared to controls had increased risk of osteoporotic fractures of the vertebrae (OR 10), hip (OR 6), and ribs or sternum (OR 3.2).⁷⁷

In a comprehensive meta-analysis van Staa et al found strong correlations between cumulative dose and bone loss and between daily dose (>5 mg prednisolone) and risk of fracture. The fracture risk increased within 3 to 6 months after the start of OCS, and decreased after stopping therapy. The increased risk remained independent of underlying disease, age and gender.⁷⁸ Later, van Staa⁷⁹ reviewed several large population based studies on fracture risk in CS users, and found consistent increased fracture risk in CS users in the hip (RR 1.61 to 2.01) and spine (RR 2.60 to 4.16). Only one study from the GPRD showed a minor increased risk for forearm fractures compared to controls (RR 1.09).⁵⁷ In a study by Angeli et al including 551 post-menopausal women given CS for different diseases, the adjusted prevalence of asymptomatic vertebral fractures was 38% for asthma/COPD.

No significant association, however, was found between fractures and CS cumulative dose or duration of therapy.⁸⁰

These studies confirm that the vertebral bodies are affected earlier and more severely than cortical bone of the long bones (radius, humerus) during OCS treatment.⁸¹ Different patterns of loss have also been demonstrated within the lumbar spine with greater damage to the trabecular bone than the cortical bone of the spinosi and apophyseal area.⁸²

Dose response relationship

There have been discussions on a threshold dose above which oral CS cause bone loss. The two large register-based studies both found increased risk for hip and vertebral fractures in a dose response relationship above daily doses as low as 2.5 mg prednisone equivalents,^{57,58} and similar results have later been demonstrated by de Vries et al⁵⁶ (Table 1). In line with this, Li et al found that COPD patients with a fracture history, reported treatment with higher doses of prednisone compared to those without fractures.⁷⁰

However, opposed to this, recent analyses of the Danish register⁸³ and the Dutch PHARMO-RLS database⁸⁴ did not find any increase in overall fracture risk for prednisolone doses <7.5 mg per day. This could be a result of less residual confounding due to adjustments for proxies for disease severity and other risk factors for fractures. A limitation of register-based studies, is lack of individual life style data, but inclusion of such data rather should weaken the association between CS use and fracture.

Increased fracture risk by duration of OCS use has been found in studies on patients with rheumatoid arthritis and lupus,^{85–87} and both Walsh⁷⁷ and de Vries⁵⁶ with coworkers have reported a substantial increased risk for fractures with increasing cumulative dose of CS. Walsh found that the highest compared to lowest cumulative quartile (median prednisolone dose 61 g versus 5 g) had an increased risk ranging from 2 for all fractures to 9 for vertebral fractures.⁷⁷

Table 1 Adjusted odds ratio for fracture risk at different sites by daily dose of prednisolone in UK General Practice Research Database (GPRD) and Danish large register studies

Prednisolone daily dose	Danish register study Vestergaard et al ⁵⁸			GPRD study Van Staa ⁵⁷		GPRD study de Vries et al ⁵⁶	
	Forearm	Hip	Spine	Hip	Spine	Hip/femur	Spine
<2.5 mg	0.99 (0.89–1.09)	0.97 (0.87–1.08)	1.16 (0.95–1.41)	0.99 (0.82–1.20)	1.55 (1.20–2.01)	1.40 (1.24–1.57)	2.89 (2.47–3.39)
2.5–7.49 mg	1.14 (0.98–1.33)	1.27 (1.11–1.44)	1.54 (1.18–1.99)	1.77 (1.55–2.02)	2.59 (2.16–3.10)		
>7.5 mg	1.19 (0.99–1.43)	1.45 (1.25–1.69)	2.08 (1.54–2.79)	2.27 (1.94–2.66)	5.18 (4.25–6.31)	2.17 (1.87–2.51)	4.00 (3.29–4.86)

Notes: The Danish study comprised 124,655 subjects having sustained a fracture during the year 2000 compared to matched controls.⁵⁸ The GPRD study by van Staa comprised 244,235 oral corticosteroid (OCS) users compared to matched controls aged ≥ 18 years. Respiratory disease accounted for 40% of treatment indications.⁵⁷ The GPRD-study by de Vries comprised 191,752 subjects aged ≥ 40 years who received OCS compared to past users of CS.⁵⁶

Results from two RCTs, however, indicated that not the cumulative, but the daily CS dose was a strong predictor for vertebral fracture, with 60% increase in risk for each 10 mg increase in prednisolone dose.⁸⁸ Based on an administrative US database, Steinbuch et al reported dose response relationship for both duration and dose of OCS. Long and continuous use of CS resulted in a significant 5-fold increased risk of hip and 6 fold increased risk of vertebral fractures. Adding high doses of prednisolone to this, the RR increased to 7-fold for hip and 17-fold for vertebral fractures.⁸⁹

CS related bone loss is most rapid during the first 6 months of OCS treatment (on average 5%), after which there seems to be a slower but steady loss of bone (1% to 2% per year).^{90,91}

An increased risk for fractures has been shown for doses above 5 mg/day within 3 to 6 months after initiation of OCS therapy,^{78,89} and for doses of ≥ 10 mg prednisolone for less than 60 days with an increasing trend by time.⁸³ Vestergaard and coworkers also found an effect of lower doses within 60 days, but this effect did not last beyond 2 months, and was probably an effect of confounding by indication. Correspondingly, van Staa found increased fracture risk even before OCS was initiated.⁵⁷

Avoidance of continuous use has been believed to reduce adverse effects on bone.⁹² Alternate, in stead of daily use of OCS has not been found to reduce bone loss in adults.^{93,94} However, long-time sporadic use has been reported to be associated with a 2-fold increased fracture risk, compared to a 6-fold increased fracture risk in those with continuous use of OCS.⁸⁹ In a GPRD study, patients with previous cumulative dose CS ≤ 1 g with intermittent high-dose CS (daily dose ≥ 15 mg) only had a small increased risk, whilst those with a daily dose ≥ 30 mg and cumulative exposure > 5 g had a relative risk of hip/femur and vertebral fracture of 3.13 and 14.42, respectively.⁵⁶

Treatment of exacerbations is an important exposure for OCS in COPD patients. Dubois et al showed that OCS courses were associated with more harmful effects against bone compared to continuous OCS treatment regimens (> 10 mg prednisolone/day).⁹⁵ The study indicated alarming bone loss of a cumulative dose above 1 g of prednisolone equal to 2 to 3 OCS courses. Corresponding effect on lumbar BMD has been reported in asthma patients receiving more than 2.5 courses of OCS compared to fewer.⁹⁶

Reversible effect

Regaining of BMD to normal levels was found in the 1990s in patients cured for Cushing disease⁹⁷ and patients having

stopped OCS therapy.^{87,98} Newer register studies showed that the increased risk of fracture in OCS-users mostly disappeared within one year after stopping therapy, most pronounced for vertebral fractures, but even the risk for hip fractures was reduced towards baseline levels.^{57,58,83} There is a rapid decrease in fracture risk beginning already three months after stopping CS treatment,⁵⁶ but the time for fracture risk to return to normal, depend on the cumulative dose used, from 6 months after cumulative dose of less than 1 g prednisolone to at least 15 months at higher cumulative dose and daily dose above 15 mg.⁵⁶ However, at cumulative doses > 10 g there is both a thinning and perforation of the trabeculae of such an extent that bone recovery is precluded after withdrawal of CS.⁹⁹

OCS and BMD

Due to disruption of collagen structure and bone architecture, rather than demineralization by CS treatment,^{100,101} the increased fracture risk in OCS users seems to be mostly independent of BMD. This explains why adjustments for BMD have not changed substantially the relative fracture rate in OCS,¹⁰² and why CS users compared to non-users have higher risk for vertebral fractures at the same levels of BMD.⁸⁸

However, bone loss due to OCS can be measured by BMD. This was first found after short time use in patients with rheumatoid arthritis and chronic fatigue syndrome;^{98,103} a mean daily dose of 7.5 mg prednisolone for 20 weeks led to 9% increased loss in trabecular bone compared to placebo.⁹⁸ Corresponding effects of OCS on BMD are found in COPD patients.

ICS and bone

Medication for inhalation was developed in order to ensure high deposition in the airways with lowest possible systemic side effects. Even though the gastrointestinal absorption of ICS like budesonide (BUD) and fluticasone (FLU) is very low compared to BDP and triamcinolone (TCA),¹⁰⁴ the active medication deposited in the airway, will reach the systemic circulation. Adverse effects on bone could be possible, and reviewers have found reason to concern about this.^{105,106}

ICS and fractures

Randomized controlled trials (RCT)

As part of a systematic review and meta-analysis of RCT, Drummond et al included three larger studies on ICS with fractures as secondary outcome.¹⁰⁷ The studies compared combined salmeterol (SAL)/fluticasone (FLU) with each

components alone and placebo for a period of 3 years in 6,112 COPD patients,³⁶ FLU with placebo in 751 patients with moderate to severe COPD,¹⁰⁸ and BUD with placebo in 1,277 smokers with mild COPD for 3 years.⁷³ Despite use of rather high doses (FLU 500 µg twice daily and BUD 400 µg twice daily), no difference in fracture risk was found between the treatment groups. A Cochrane review of seven RCT found no effects of 2 to 3 years use of conventional doses of ICS on BMD or fracture risk, but very high doses were associated with increase in markers of bone turnover.³¹ Altogether the studies included cases with mild to severe COPD, doses considered as moderate to high, but the follow-up time was short compared to what is the case for most COPD patients.

Observational studies

Knowledge on potential effects of ICS on bone could be derived from studies including asthma patients, as these lack many of the negative life-style factors characteristic of COPD patients. Lipworth et al in 2002 reviewed available literature on ICS and systemic adverse effects published from 1966 through 1998, and found that all ICS, but especially FLU (at doses above 800 µg), exhibited dose-related adrenal suppression, a risk factor for bone loss. Data on bone turnover, however, were not included in these studies.¹⁰⁹

In 2003 Richy et al reviewed all controlled trials having data on ICS, and BMD/markers/fractures in asthma, COPD and healthy persons.¹¹⁰ Data from the included studies showed that all considered ICS, compared with placebo or controls, appeared to affect bone markers or lumbar BMD in asthma, COPD or in healthy adults, but the study lacked power to investigate fracture risk. TCA led to the most deleterious effects on bone, followed by BDP and BUD. There was a dose response relationship, both regarding daily dose and duration of ICS use, and bone loss. Assuming a linear bone loss in CS-induced osteoporosis, use of TCA 1 mg/day during 20 years would lead to an estimated 6.7% decrease in BMD compared with unexposed asthma or COPD controls, whereas corresponding figure for BUD would be 2.4%. However, as the authors discussed, there might be not-linear time-effect model due to compensatory mechanisms in patients exposed to ICS on a long-term basis. Furthermore, two of the studies^{73,111} included specifically smokers, who were older than in the other studies. Excluding these, rendered the results non-significant, suggesting that an effect of aging, smoking and higher cumulative dose of ICS might have influenced the results.

Based on the Danish register, Vestergaard et al found a limited increase in the risk of any fracture, but not hip,

spine or forearm fractures, in ICS-users of more than 7.5 mg prednisolone equivalents per day (equivalent to 1875 µg of BUD per day).⁵⁸ Van Staa et al based on GPRD data, four years earlier, had reported increased risk for fracture at all these sites, and even in a dose-response relationship effect by ICS. However, they did neither find differences in fracture risk between the ICS and bronchodilator groups compared with non-users, nor between users of different ICS (BUD, FLU and BDP).¹¹² Restricting a study to elderly women in the same database, Hubbard et al, found ICS-use to be associated with increased fracture risk (OR 1.19 adjusted for OCS) and in a dose response relationship.¹¹³ Including disease severity indicators as confounders in a study from the same database, de Vries et al found that the crude two-fold fracture risk at the hip in patients on high dose ICS (>1.6 mg) was reduced to similar risk as non-users of ICS,⁶⁶ and later they found similar result in a Dutch study.⁸⁴

However, even recent studies have reported a small increase in fracture risk by ICS, but mainly with use of higher doses.^{71,114,115}

CS have less influence on appendicular bone than hip and spine. Even so, in a cross-sectional population-based study in Norway, current users of only ICS had 2% lower forearm BMD compared to ICS-naïve individuals, and additional use of OCS was associated with 8% lower BMD.¹¹⁶ Similar results were found during a follow-up study for 5 years,¹¹⁷ but despite the possibility to adjust for both diseases severity, other risk factors and individual life style factors, lack of any dose response relationship between ICS-use and BMD, could indicate confounding by disease severity.

The studies do not fully preclude adverse effects of at least high dose ICS on bone, but what is the clinical relevance of such an effect? Weatherall et al addressed this in a recent systematic review and meta-analysis of 5 case-control studies of ICS use.¹¹⁸ The random-effects odds ratio of relative risk for a non-vertebral fracture was 1.12 (95% confidence interval 1.00 to 1.26) per 1.0 mg increase in the daily dose of BDP or equivalent. This risk was considerably less than other common risk factors for fracture in the older adult, with figures of: 1 or more falls 4.7, use of antipsychotic medication 2.8, body mass index <18.5 kg/m² 2.4, cerebrovascular disease 1.9, use of hypnotic medication 1.7, and being a current smoker 1.5.¹¹⁸

What dose level of ICS is used in COPD?

Mild asthma is very responsive to CS, and most of the therapeutic effect of ICS is obtained at doses around 400 to 500 µg of BDP equivalents, with the mean dose achieving

the maximum benefit being around 1,000 µg/day.^{119,120} CS suppress the multiple inflammatory genes that are activated through recruitment of the enzyme histone deacetylase 2 (HDAC2). Smoking, however, contributes to steroid resistance¹²¹ through negative effect on HDAC2.¹²² Hence, for optimal CS response, COPD patients and smoking asthma patients need higher CS doses compared with non-smokers. As the introduction of ICS combined with LABA in asthma patients has led to asthma control at lower ICS doses,¹²³ the concern for negative effects on bone among these patients are minimized compared to smokers with asthma or COPD. Even though significant differences between single ICS and combination therapy on BMD and bone metabolism markers were not found, a study indicated more favorable pattern for the combination therapy.¹²⁴

RCTs on the effect of ICS on different outcomes in COPD patients have mostly used higher doses of ICS than is generally used in asthma patients. Daily doses of FLU have been 500 µg twice daily,^{36,108,125–128} BUD 320 to 400 µg twice daily,^{73,129–131} and TCA 1,200 µg/day.¹¹¹ Recently, however, Ferguson et al published a RCT reporting a similar reduction in annual rate of exacerbation by FLU/SAL 250/50 µg/mg twice daily (30% compared with SAL) as reported in previous studies of double ICS dose.¹³² Two other studies of shorter duration (24 weeks) showed that FLU/SAL 250/50 bid improved lung function and reduced severity of dyspnea compared with individual components and placebo, but these had not power to study exacerbations.^{133,134} Further studies on defining the lowest dose needed to reach the desirable effects of ICS are therefore warranted. Today there is a discrepancy between the size of doses used in the majority of studies and doses prescribed in the clinic. In the US, higher doses than FLU/SAL 250/50 and BUD/FOR 320/9 µg/mg twice daily are currently not approved for use in COPD.

For CS exposure during exacerbations, Stallberg et al in a RCT found no difference between 2 weeks of high-dose BUD/FOR combination and prednisolone 30 mg.¹³⁵ Even if all patients were given one dose of prednisolone 30 to 50 mg before randomization, the total CS exposure in those getting ICS would be about one-third of those receiving OCS.

Bone turnover and influence of inflammation

In all individuals there is a continuous bone remodeling, and in adults about 25% of trabecular and 3% of cortical bone are replaced each year.¹³⁶ Central cells in this balance are osteoclasts, which resorb bone, and osteoblasts, which replace lost bone with new matrix, which

subsequently mineralizes. Osteocytes and their canicular network serve as mechanosensors, and play a role in the repair of bone microdamage.¹³⁷ There is a close interaction between osteoblasts and osteoclasts, mainly mediated by receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG). RANKL is expressed on the surface of osteoblasts, and its expression increases in response to different pro-resorptive signals such as proinflammatory cytokines, CS, estrogen deficiency and excess of parathyroid hormone.¹³⁸ RANKL is the critical stimulator of the differentiation and activity of osteoclasts leading to bone resorption. OPG is a decoy receptor that is secreted by osteoblasts and reduces bone resorption by binding to RANKL.^{139,140}

The influence of inflammatory diseases on bone is thoroughly discussed in a recent review by Hardy and Cooper.¹⁴⁰ Shortly, inflammatory cells also express or secrete RANKL, or produce cytokines (TNF-α and interleukins) promoting bone resorption independent of osteoblasts.¹⁴¹ Why increased bone resorption is not followed by bone formation is unclear, but at least TNF-α inhibit the differentiation of osteoblasts.¹⁴²

Interestingly, inflammation modifies the action of the enzymes, 11β-hydroxysteroid dehydrogenases (11β-HSDs) responsible for the intracellular CS metabolism. One of these converts inactive CS such as cortisone and prednisone to their active counterparts cortisol and prednisolone. Exposure to proinflammatory cytokines increases the levels of autocrine generated cortisol in the osteoblasts, leading to decreased bone formation through direct effect on osteoblasts, as well as increased osteoclast activity due to upregulation of RANKL and downregulation of OPG.^{139,143} The 11β-HSDs might contribute to the individual heterogeneity in the response to CS therapy. A common polymorphism in the efflux transporter P-glycoprotein which is associated with CS sensitivity might also confer susceptibility to CS-induced osteoporosis.¹⁴⁴

The pathogenesis of CS-induced osteoporosis

Figure 2 shows the bone cells and mechanisms being involved in CS-induced bone loss. The loss occurs in two phases, a rapid early phase, probably due to excessive bone resorption, and a slower, progressive phase due to impaired bone formation.^{145,146} In the first phase CS increase the expression of RANKL and macrophage colony stimulating factor, while decreasing the expression of OPG in stromal and osteoblastic cells, thereby favoring osteoclast differentiation and bone resorption.¹³⁹ Furthermore, CS decrease the apoptosis of mature osteoclasts leading to a prolonged bone resorption.¹⁴⁷

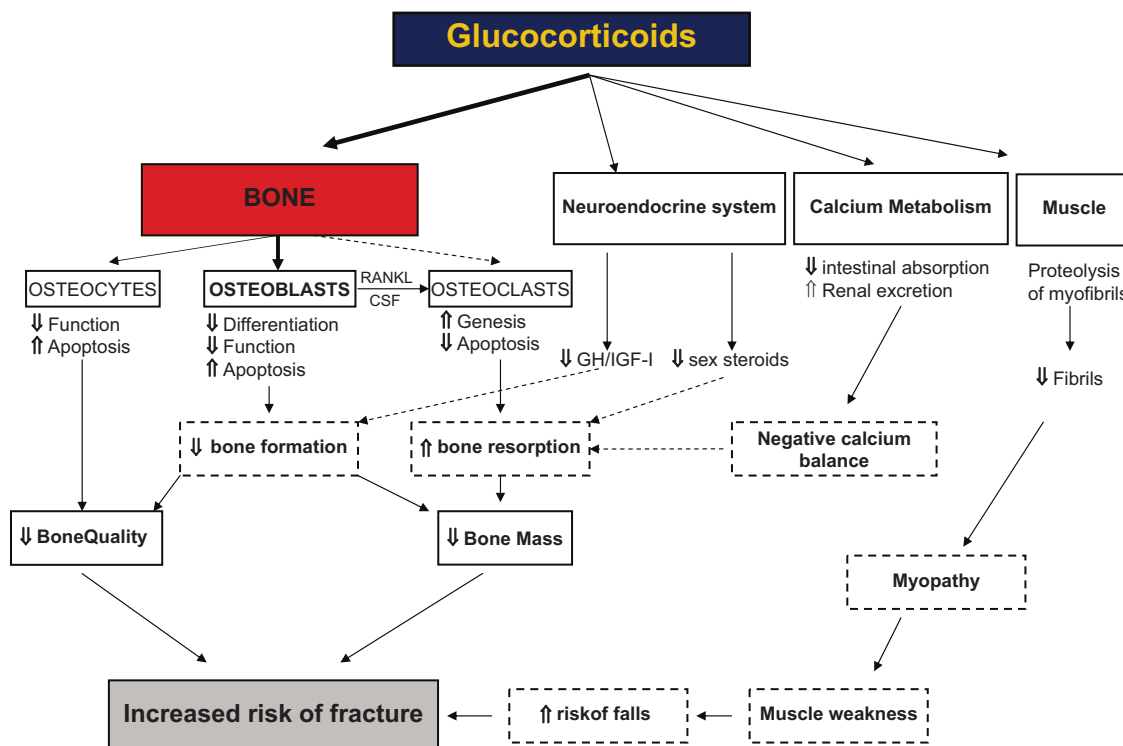


Figure 2 Diagram showing the direct and indirect effects of glucocorticoids on bone leading to glucocorticoid-induced osteoporosis and fractures. Reproduced with permission from Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int*. 2007;18(10):1319–1328.¹⁴⁹ Copyright © 2007 Taylor & Francis.

The excess resorption, however, falls with long-term CS, probably due to inhibition of differentiation of osteoclast precursors.¹⁴⁷

In the second phase, inhibition of proliferation, differentiation as well as maturation of osteoblasts, lead to impairment of bone formation.^{148,149}

CS also exert negative effects on osteocytes by disturbing their mechanosensor function and inducing apoptosis.¹⁵⁰ This reduces the strength of bone, independently of changes in bone remodeling and architecture,¹⁵¹ and might partly explain why patients treated with CS experience fractures at a higher BMD level than non-CS users. Additionally, CS have an indirect, negative effect on bone formation by reducing the expression of insulin like growth factor (IGF)1.¹⁴⁵ Low levels of gonadal steroids increase bone resorption.¹⁵² However, even though CS decrease the level of these hormones, the adverse effects are still observed in patients with maintained menstrual cycle activity implying that the adverse effects of CS are largely independent of hypogonadism.¹⁵³

Secondary hyper-parathyroid state, due to the effects of CS as inhibitors of calcium absorption from the gastrointestinal tract and calcium reabsorption in the renal tubuli, has been

postulated, but studies have not reported association between CS and increased parathyroid hormone.¹⁴⁵

Other pathophysiological mechanisms are discussed, among these, redirection of differentiation of bone marrow stromal cells from cells of the osteoblastic lineage to the adipocyte lineage,¹⁴⁵ and inhibition of osteoblast differentiation by opposing Wnt- β -catenin signaling.¹⁵⁴ The relative importance of the various components is not yet known.

CS initially mainly affect trabecular bone due to higher metabolic activity, but with prolonged use cortical bone is also affected.¹⁴⁶ Muscle weakness and atrophy is also a consequence of OCS treatment. The changes particularly involve the pelvic girdle musculature, with less involvement of the shoulder girdle and distal musculature. It generally occurs within weeks to months after initiation of OCS. In stable patients with COPD, a 2-week course of 30 mg prednisolone was not associated with muscle weakness.¹⁵⁵

Osteoporosis and fractures associated with other medication

Bronchodilators

Overstimulation of the adrenergic system has been associated with a low BMD or increased bone fragility,¹⁵⁶

and according to experimental studies, activation of the β_2 -receptors on osteoblasts leads to production of RANKL resulting in increased osteoclastogenesis and reduced BMD.¹⁵⁷ Bonnet et al showed that the β_2 -agonists salbutamol and clenbuterol reduced bone mineral content and increased the level of bone resorption markers. Opposed to clenbuterol, however, salbutamol did not seem to have any effect on bone microarchitecture or anabolic effect on muscles. Corresponding to these results, a meta-analysis of 7 studies assessing fracture risk in patients using β -blockers concluded that their use was associated with a 28% reduction in hip fracture risk and a 14% reduction in the risk for any fracture.¹⁵⁸

Use of convenient doses of β_2 -agonists probably does not affect bone. In 2 large case-control studies increased risk of fractures associated with β_2 -agonist treatment was found.^{159,160} Adjustments for use of OCS and disease severity, substantially reduced the excess risk found in β_2 -agonist users, and causal effect of the latter seems unlikely as there was no dose dependent relation between use of inhaled short-acting β_2 -agonists and fractures, in as much oral β_2 -agonists were associated with an increase in fracture risk at low, but not higher doses.¹⁶⁰

A study in rats indicated that theophylline treatment promoted skeletal calcium loss,¹⁶¹ and some effect on bone turnover markers were reported in a study including patients with mild asthma on theophylline treatment.¹⁶² However, no increased fracture risk by theophylline was found in a study by Vestergaard et al,¹⁶⁰ and for anticholinergics, de Vries et al found similar risk of hip/femur fracture between users of β_2 -agonists, ICS and anticholinergics,¹⁵⁹ indicating these effects to be caused by underlying disease instead of medications. Anticholinergics and theophylline might have beneficial effects on systemic inflammation and comorbidities of COPD, but this is not proven yet.⁴ Interestingly, low-dose theophylline might also reverse CS resistance in COPD.

Risk estimation

Prior presence of other important risk factors enhances the adverse effects on bone by life style, COPD itself and treatment, and bone densitometry should be considered (Table 2). For patients having lost height the possibility of undiagnosed vertebral compression fractures should be considered.

Thresholds for treatment of osteoporosis previously have been at fixed T-scores given by bone densitometry. Opposed to postmenopausal osteoporosis with a recommended threshold at T-score -2.5 SD for initiating of treatment, the threshold in patients on CS treatment should be higher due to the

Table 2 Dual energy absorptiometry measurements – recommendations

- Generally
 - Sites: hip and lumbar spine
 - Women ≥ 65 years and men ≥ 70 years¹⁶⁴
 - Younger postmenopausal women and men aged 50 to 69 years in case of one major or two minor risk factors for osteoporosis¹⁶⁴
- Ideally, all patients starting with OCS, but at least:
 - Start of OCS with daily dose ≥ 5 mg for ≥ 3 months
 - Need of ≥ 1 OCS course yearly¹⁶⁷
- Measurement interval
 - 5 years if no risk factors or CS therapy¹⁰
 - 2 years or more to follow loss or treatment effect
 - 1 year if use of OCS without anti-resorptive treatment

Abbreviations: CS, corticosteroids; OCS, oral corticosteroids.

adverse effect on bone not reflected by bone densitometry. The American College of Rheumatology has set cut off at -1 compared to -1.5 SD in the UK guidelines.¹⁶³ This is supported by current evidence of CS effect on bone, and encourages more focus on estimation of absolute long-term fracture probability.

Many osteoporosis risk-assessment tools have been developed,¹⁶⁴ and WHI Hip Fracture Risk Calculator (www.hipcalculator.fhcrc.org) and the FRAX tool (www.shef.ac.uk/FRAX), for example, could be useful supplements to BMD assessments.^{164,165} However, the tools are based on cohort studies, and the data might not be representative for all populations. Further, there is limited increase in risk score compared to use of BMD alone. For example, at age 50 the gradient of hip fracture risk per SD change in risk score was 2.0, 3.68 and 4.23 with use of clinical factors, BMD and both, respectively.¹⁶⁶

Recommendations for treatment of COPD patients

Health care professionals ought to be well aware of adverse effect on bone from CS therapy, but risk evaluation is performed to a limited extent. In a US study in 2002 of osteoporosis intervention in patients on CS treatment, bone densitometry was performed in 9% of men and 27% of women exposed to OCS and in 4% of men and 23% of women exposed to ICS.¹⁶⁸

One important aspect of COPD treatment should be to avoid bone loss and fragility fractures. This involves change in life style, treatment to allow for increased physical activity, keep CS exposure as low as possible, Calcium and vitamin D and anti-resorptive therapy (Table 3). An important challenge

Table 3 Recommendations for prevention and treatment of osteoporosis in COPD patients

- Avoid further bone loss
 - Smoking cessation
 - Weight-bearing and strengthening exercise
 - Adequate nutrition
 - Maintain weight if not overweight
 - Rehabilitation programs in moderate to severe disease¹⁶⁹
- COPD – treatment
 - Long-acting bronchodilators to all patients where airway obstruction might limit the level of physical activity¹⁷⁰
 - ICS or ICS/LABA or long-acting anticholinergics in severe COPD in order to reduce frequency of exacerbations
 - Reduce CS exposure by:
 - Maintenance therapy: ICS in moderate doses
 - Exacerbations: Consider dependent on the individual patient:
 - A. Lower OCS dose (30 mg prednisolone for 7 to 8 days)
 - B. High-dose ICS/LABA after one dose of prednisolone 30 mg¹³⁵
- Calcium and vitamin D (1200 mg and 800 IU, respectively)¹⁷²
 - To everyone aged 50 years or more
 - If start with OCS or high-dose ICS
- Bisphosphonates
 - If daily dose of CS ≥ 5 to 7.5 mg and T-score < -1 (-1.5)
 - If yearly cumulative dose of CS > 800 mg prednisolone
 - If previous fragility fracture and T-score < -2.5 if no use of CS
- Estrogen
 - Consider in hypogonadal premenopausal women exposed to CS
- PTH analogues
 - Consider in CS users with high risk of fractures

Abbreviations: CS, corticosteroids; ICS, inhaled corticosteroids; OCS, oral corticosteroids; LABA, long-acting β_2 -agonist.

is to succeed in communication with all COPD patients. Especially, lower socioeconomic classes have high prevalence of COPD, but also less adherence to behavior advice.

Calcium and vitamin D supplementation reduce fracture risk,¹⁷¹ and early start reduced fracture risk by 12% in one study.¹⁷² Interestingly, a dose-dependent association between vitamin D levels and pulmonary function has been found, and vitamin D supplement might extend beyond the protective effect on bone, and influence the inflammation in the lungs and interfere with co-morbidities of COPD.⁴⁹

Sex hormone treatment also reduces fracture risk.¹⁷¹ Estrogen preserves bone in post-menopausal women independently of CS use,¹⁷³ but its use is currently limited due to concern for side effects like cardiovascular disease and breast cancer. Such treatment, however, should be considered in hypogonadal premenopausal women exposed to CS, because of limited experience with bisphosphonates beyond 10 to 12 years.^{164,174}

Anti-resorptive therapy should be considered early during OCS treatment, as increased bone loss starts immediately after the beginning of treatment in a daily dose relationship.¹⁷⁵ Bisphosphonates have been reported to be the most effective of evaluated agents for managing CS-induced osteoporosis, and this effect is enhanced further with concomitant use of vitamin D and calcium.¹⁷⁶ There is strong evidence of reduced fracture risk for most of the bisphosphonates, including the intra-venous alternative zoledronic acid.¹⁷¹ The main effect of bisphosphonates is the inhibition of bone resorption, but they have also been shown to prevent osteoblast and osteocyte apoptosis,¹⁷⁷ and could thereby preserve the integrity of the osteocyte network and the osteoblast lifetime.

The American College of Rheumatology recommends bisphosphonates in all men and postmenopausal women in whom long-term (>3 months) CS treatment with daily dose ≥ 5 mg is initiated, and if T-scores at the spine or hip are below -1 SD independent of OCS dose.¹⁷⁴ The UK guidelines suggest this treatment in patients with high risk for osteoporosis; users of ≥ 7.5 mg OCS, previous experience of a fragility fracture or other risk factors for osteoporosis. Among patients with low risk of osteoporosis, anti-resorptive treatment should be considered if T-score < -1.5 SD or decline in vertebral BMD $\geq 4\%$ after 1 year of CS treatment,¹⁶³ Vestergaard et al recommended fracture prevention independent of BMD status in patients reaching a yearly cumulative dose of about 800 to 900 mg prednisolone.⁸³ This equals 2 courses of prednisolone or a daily dose of 2.5 mg prednisolone for 1 year.

Anabolic drugs like the parathyroid hormone analogue teriparatide stimulate bone formation through effects on osteoblasts and osteocytes, and may therefore more directly target the main pathophysiological mechanism in CS induced osteoporosis. Teriparatide has been found to be superior to alendronate in CS-induced osteoporosis, both regarding change in BMD and morphometric vertebral fractures,^{178,179} but there is so far weak evidence for hip fracture reduction.¹⁷¹ In post-menopausal women with osteoporosis, strontium ranelate also has been found to reduce fracture risk.¹⁸⁰ The treatment has combined anabolic and anti-catabolic effect, in addition to effect on BMD due to incorporation of strontium into hydroxyapatite instead of calcium. This strengthens the correlation between increase in BMD and reduction in fracture risk, compared to other osteoporosis therapies, and might thereby increase the value of follow-up BMD as a marker of therapeutic efficacy. However, studies of the effect of strontium ranelate in CS-induced osteoporosis have not been published.¹⁸⁰

Conclusions

Among available treatments for COPD, only CS-treatment has documented adverse effects of clinical significance. CS have both direct adverse effects on bone and indirect effects due to muscle weakening and atrophy. These effects are dose dependent both regarding daily dose, duration and cumulative dose. Less negative effects are seen by sporadic compared to continuous use, but lower continuous doses have less detrimental effects on bone than frequent high-dose course of OCS. High doses of ICS seem to increase bone loss, but the extent of this effect is discussed because it is difficult to differentiate between the effect of ICS dose used, other risk factors, prior or concomitant use of OCS and not at least, disease severity. The health care should increase focus on healthy lifestyle and use of limited CS doses, as well as be aware of potential osteoporosis development in this group of patients. Studies on the effectiveness of use of long-acting anticholinergics or use of combinations with moderate ICS doses in severe COPD are warranted, as well as development of new anti-inflammatory drugs with specific effects on COPD inflammation and minor adverse effect on bone.

Disclosures

Dr Arnulf Langhammer is the project leader of the Lung Study in the Nord-Trøndelag Health Study (HUNT). The Lung Study was partly funded through a non-demanding grant from AstraZeneca Norway in 1995–97 (HUNT 2) and 2006–08 (HUNT 3). AstraZeneca is the producer of the ICS budesonide and the long-acting β_2 -agonist formoterol. He has also received salaries as a speaker and member of advisory boards for many different pharmaceutical companies. Additionally, in his work as general practitioner, he has participated in many multi-center studies for pharmaceutical companies. In medical practice he is joint-owner of a DXA bone densitometer.

Dr Siri Forsmo declares no conflicts of interest.

Dr Unni Syversen has received salaries as a speaker and member of several advisory boards for different pharmaceutical companies and has also participated in multicenter trials for several pharmaceutical companies.

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