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REVIEW

Long-term use of inhaled glucocorticoids in patients with stable chronic obstructive pulmonary disease and risk of bone fractures: a narrative review of the literature

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Abstract: Patients with chronic obstructive pulmonary disease (COPD) demonstrate a greater osteoporosis prevalence than the general population. This osteoporosis risk may be enhanced by treatment with inhaled corticosteroids (ICSs), which are recommended for COPD management when combined with long-acting bronchodilators, but may also be associated with reduced bone mineral density (BMD). We conducted a narrative literature review reporting results of randomized controlled trials (RCTs) of an ICS versus placebo over a treatment period of at least 12 months, with the aim of providing further insight into the link between bone fractures and ICS therapy. As of 16 October 2017, we identified 17 RCTs for inclusion. The ICSs studied were budesonide (six studies), fluticasone propionate (five studies), mometasone furoate (three studies), beclomethasone dipropionate, triamcinolone acetonide, and fluticasone furoate (one each). We found no difference in the number of bone fractures among patients receiving ICSs versus placebo across the six identified RCTs reporting fracture data. BMD data were available for subsets of patients in few studies, and baseline BMD data were rare; where these data were given, they were reported for treatment groups without stratification for factors known to affect BMD. Risk factors for reduced BMD and fractures, such as smoking and physical activity, were also often not reported. Furthermore, a standardized definition of the term "fracture" was not employed across these studies. The exact relationship between long-term ICS use and bone fracture incidence in patients with stable COPD remains unclear in light of our review. We have, however, identified several limiting factors in existing studies that may form the basis of future RCTs designed specifically to explore this relationship.

Keywords: COPD, inhaled corticosteroids, osteoporosis, fracture risk

Plain language summary

Osteoporosis, a condition that causes bones to become fragile and prone to fracture, is more common in patients with chronic obstructive pulmonary disease (COPD) than the general population. In addition, inhaled corticosteroids (ICSs), which are recommended for COPD treatment alongside other agents, may also have a negative effect on bone strength and may further increase fracture risk for these patients. Previous studies looking at the association between ICS use and bone fracture risk have given mixed results, meaning that this potential relationship must be explored further. We present the results of a review of published studies of ICS versus placebo in patients with COPD lasting at least 12 months, with the hope of identifying further details of the ICS-bone fracture relationship. We found no difference in the fracture risk for patients receiving ICSs compared with those receiving placebo. Our

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review did, however, identify issues in the reporting of bone data in the studies we identified, including limited reporting of known risk factors for fractures (smoking, exercise) and a lack of a standard definition of the term "fracture" across the studies. Further research into the relationship between ICS treatment and bone fractures is needed to determine the potential impact for patients with COPD.

Introduction

Current national and international guidelines for the management of patients with chronic obstructive pulmonary disease (COPD) recommend maintenance therapy with inhaled long-acting bronchodilators (long-acting β_2-adrenergic agonists [LABAs] and long-acting muscarinic antagonists [LAMAs]), inhaled corticosteroids (ICSs), including glucocorticoids, and their combinations (usually LABA/ICS in one single inhaler at fixed dose) for the treatment of moderate-to-severe disease.[1–5] In addition, patients with COPD may experience exacerbations requiring short-term treatment with systemic corticosteroids,[2] which may increase their risk of developing osteoporosis through effects exerted on osteoclasts and osteoblasts.[6] Coupled with the already increased prevalence of osteoporosis among patients with COPD,[7] treatment with ICSs may substantially increase the risk of bone fractures in this patient population.

The skeletal effects of ICSs are not fully understood and existing studies provide conflicting results; however, most studies in patients with COPD receiving ICSs have not found a detrimental effect of these agents on bone.[8] Our understanding of this topic is hindered by the reporting of incomplete and inconclusive data on baseline bone mineral density (BMD) in patients with stable COPD receiving long-term, regular treatment with ICSs in published studies. Baseline BMD data were available for a subgroup of 658 patients from the TORCH study; these data demonstrated a high prevalence of osteoporosis at baseline in stable COPD patients, and no significant difference was observed in the risk of developing osteoporosis and/or bone fractures after 3 years of therapy with fluticasone propionate alone versus placebo.[9]

Two meta-analyses on the risk of bone fractures with ICSs in COPD patients have been published to date, and, unlike in the BMD-evaluable patients of the TORCH study, both reported an increased likelihood of bone fractures in patients receiving ICSs.[10,11] Yet, only one of these meta-analyses produced a result with statistical significance (P=0.04 for a relative increase of more than 20% in the likelihood of bone fractures in COPD patients receiving ICSs),[10] and both analyses were associated with a number of inherent limitations. The most recent systematic review on the role of ICSs in the long-term treatment of COPD patients was conducted by the Cochrane Collaboration group and concluded that, in long-term studies in which the effect of ICSs on bone density was measured, no notable effects on bone density and bone fractures were apparent during a 3-year follow-up period.[12] This observation, however, was based on a small number of studies.

Given the mixed results obtained in previous meta-analyses and reviews on this topic, and the limitations associated with each, further exploration of the association between ICS use and bone fractures in COPD is necessary. The aim of our narrative review was to measure the risk of bone fractures in patients with COPD enrolled in long-term (at least 12 months' duration) randomized controlled trials (RCTs) of inhaled glucocorticoids alone versus placebo. We chose not to include studies using a combination of glucocorticoids and LABAs or LAMAs because of their potential effects on bone metabolism.[13–19]

Methods

Search strategy

A targeted, structured literature search was conducted using the PubMed database (NCBI, Bethesda MD, USA) using the search terms ["inhaled corticosteroids" and "COPD"] and ["bone mineral density" OR "hip fractures" OR "spinal fractures" OR "bone fracture(s)" OR "bone loss" OR "osteoporosis" OR "corticosteroid osteoporosis" OR "bone densitometry" OR "bone metabolism"]. The search was restricted to capture only full manuscripts published in English. Publications reporting the results of RCTs studying the long-term (≥12 months) use of ICS alone versus placebo in patients with stable COPD (no documented exacerbation history) were selected by two investigators, Fabio Arpinelli and Maria Sandra Magnoni.

COPD studies using agents other than ICSs (eg, an ICS/LABA combination) were excluded due to the potential effects of other agents on bone metabolism. Observational studies were excluded due to the potential inclusion of confounding variables in populations retrieved from health databases.

Data extraction

Key data were extracted from all eligible studies by a single investigator. Data on the following aspects of the studies were collected: study design variables (number of patients,

length of ICS treatment); patient characteristics (age, gender, previous therapies, smoking, ethnicity, bone fractures, and BMD where available); and outcomes of interest.

Results

Search results

A total of 128 studies reported RCTs of patients with stable COPD published as full papers in English. These studies were filtered further to include those lasting between 12 and 48 months (n=32) and to include only those that compared ICS with placebo (n=17), giving a final total of 17 studies (Figure 1). These 17 studies were chosen for inclusion in our review (Table 1).

The ICSs used in each study were as follows: budesonide in six studies;[20–25] fluticasone propionate in five studies;[9,26–29] mometasone furoate in three studies;[30–32] beclomethasone dipropionate,[33] triamcinolone acetonide,[34] and fluticasone furoate[35] in one study each. Bone density was reported for subsets of patients in two studies,[21,34] and bone fractures were reported for six studies.[9,21,26,30,31,35] The majority of the identified RCTs were conducted in European countries only (10/17).

Patient characteristics

The proportion of males was higher than females in all included studies (male:female ratio range 1.08–6.21) and two studies enrolled only males.[22,26] Mean age ranged from 46 to 67.6 years across all treatment arms in all studies.

Bone mineral density

Baseline and 3-year BMD data of the hip and lumbar spine were published by Ferguson et al for a subset of 658 American patients from the TORCH population (n=6,184). At baseline, 18% of men and 30% of women had osteoporosis; when based on BMD assessment, osteopenia was present in 42% and 41% of men and women, respectively. After 3 years of treatment, changes in BMD at the hip and lumbar spine were small, and no significant difference between fluticasone propionate and placebo was found (−2.9% and −3.1%, respectively). The incidence of bone fractures was also low and similar for all treatments (5.1–6.3% across all arms).[36]

BMD was also measured in a sample of 194 patients (102 receiving budesonide and 92 in the placebo arm) in the EUROSCOP study. There was a significant change over time and no significant effect of treatment on BMD, except for a small, significant difference at the femoral trochanter (BMD decline in the femoral trochanter was 0.38% in the placebo arm and 0.04% in the budesonide arm [P=0.02]).[21]

Of the 1,116 patients of The Lung Health Study, BMD data for the lumbar spine and femur were taken for 412 patients. No significant differences were detected at baseline. After 3 years, the BMD of lumbar spine and the

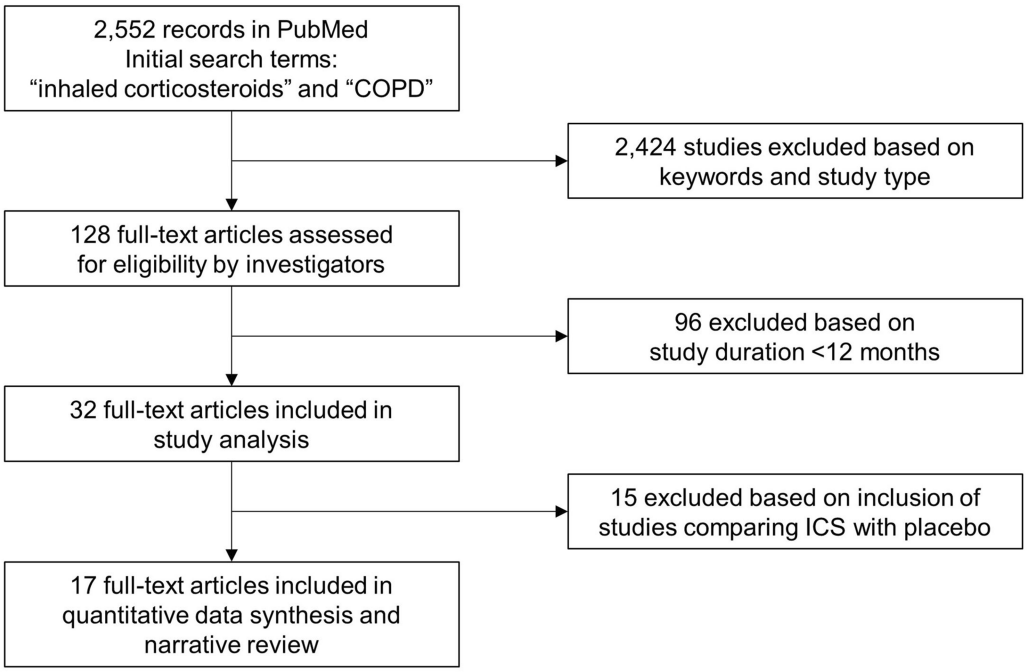

Figure 1 Flow chart of study selection.

Table 1 Characteristics of RCTs

Reference	Number of pts, length of ICS therapy (months), previous use of OCS and/or ICS	Mean age	Gender (%)	M/F ratio	% current and ex-smokers	Definition of former smokers	Ethnicity	Geographic area	Mean FEV_1 (pre-post bd) absolute value in liters (% predicted)	ICS and dosage	Baseline bone mass density	Vit D before	Vit D during	Bone fractures
Renkema et al, *Chest* 1996[22]	58 24 No	Bud 56 Bud+Pred 58 pla 54	m (100%)	0	cs Bud 43 Bud +Pred 47 pla 44	Stopped smoking at least 1 year before	nr	Netherlands	Pre bd Bud 2.16 L (67%) Bud+Pred 1.86 L (61) pla 1.90 L (60)	Bud 1,600 μg/d Bud+Pred 1,600 μg/d +5 μg/d	nr	nr	nr	nr
Vestbo et al, *Lancet* 1999[25]	290 36 No in previous 6 months	Bud 59 pla 59.1	Bud m 58.6 pla m 62.1	1.52	cs Bud 75.9 pla 77.2	nr	nr	Denmark	Post bd Bud 2.36 L (86.2) pla 2.39 L (86.9)	Bud 1,200 μg/d (6 months), then Bud 800 μg/d (30 months)	nr	nr	nr	nr
Weir et al, *Clin Exp Allergy* 1999[33]	98 24 No	BdP 65.5 pla 67.6	BdP m 65.3 pla m 83.6	2.92	cs BdP 34.7 pla 42.8 es BdP 63.2 pla 57.1	nr	nr	UK	BdP pre bd 1.07 L (39.7) Post bd1.19 L pla Pre bd 1.13 L (41.4) Post bd 1.26 L	BdP 750 μg bid <50 kg 1,000 μg bid >50 kg	nr	nr	nr	nr
Pauwels et al, *N Engl J Med* 1999[21]	1,277 36 No in previous 6 months	Bud 52.5±7.5 pla 52.4±7.7	Bud m 73.5 pla m 72.2	2.60	100	nr	nr	Belgium, Denmark, Finland, Italy, Netherlands, Norway, Spain, Sweden, UK	Pre bd Bud 2.53±0.64 L (76.8) pla 2.54±0.64 L (76.9)	Bud 400 μg bid	Measured on 194 subjects. No change over time and no effect of treatment on bone density, except for a small, significant difference at the femoral trochanter in favor of budesonide	nr	nr	Baseline Vertebral Bud 13.4%; pla 11.5% End study Bud +8; pla +3 (P=0.50)

(*Continued*)

Table 1 (Continued).

Reference	Number of pts, length of ICS therapy (months), previous use of OCS and/or ICS	Mean age	Gender (%)	M/F ratio	% current and ex-smokers	Definition of former smokers	Ethnicity	Geographic area	Mean FEV_1 (pre-post bd) absolute value in liters (% predicted)	ICS and dosage	Baseline bone mass density	Vit D before	Vit D during	Bone fractures
Lung Health Study Research Group, *N Engl J Med* 2000[34]	1,116 40 (mean) No in previous year	TA 56.2±6.8 pla 56.4±6.8	TA f 36% pla f 37.9%	1.70	cs TA 90.5 pla 89.8	Smoking cessation for over 2 years	Non-white TA 6.3% pla 4.1%	USA	TA pre bd 2.16 L (65) Post bd 2.28 L (68.5) pla pre bd 2.10 L (63.4) Post bd 2.22 L (67.2)	TA 600 μg bid	Measured at lumbar spine on 328 subjects, and at femoral neck on 359 subjects. After 3 years higher percentage decrease of bone density in those taking TA	nr	nr	nr
Burge et al, *BMJ* 2000[26]	751 36 FP 51% pla 57%	FP 63.7 pla 63.8	FP m 75 pla m 74	2.93	cs FP 36.4 pla 39.2 es FP 46.8 pla 45.8	nr	nr	UK	Post bd FP 1.42 L (0.47) pla 1.40 L (0.49)	FP 500 μg bid	nr	nr	nr	FP 9 pla 17 2% both groups
Calverley et al, *Lancet* 2003[27]	1,465 12 nr No in 4 weeks prior to study	FP 63.5 pla 63.4	FP m 70 pla m 75	2.61	cs FP 47 pla 53	nr	nr	UK	FP pre bd 1.26 L (45.0) Post bd 2.36 L pla 1.27 L (44.2) pla post bd 1.38 L	FP 500 μg bid	nr	nr	nr	nr
Calverley et al, *Eur Respir J* 2003[20]	1,022 12 nr	Bud 64 pla 65	Bud m 74 pla m 75	3.07	cs Bud 39 pla 30	nr	nr	Africa, Asia, Europe	Bud 1±0.32 L (36) pla 0.98 ±0.33 L (36)	Bud 400 μg/d	nr	nr	nr	nr

(*Continued*)

Table 1 (Continued).

Reference	Number of pts, length of ICS therapy (months), previous use of OCS and/or ICS	Mean age	Gender (%)	M/F ratio	% current and ex-smokers	Definition of former smokers	Ethnicity	Geographic area	Mean FEV_1 (pre-post bd) absolute value in liters (% predicted)	ICS and dosage	Baseline bone mass density	Vit D before	Vit D during	Bone fractures
van Grunsven et al, *Respir Med* 2003[29]	48 24 nr	FP 46 pla 47	FP m 50% pla m 54%	1.08	cs FP 50 pla 50	nr	nr	Netherlands	FP pre bd 3.05 L (95) Post bd 3.16 L (98) pla pre bd 3.17 L (98) Post bd 3.19 L (99)	FP 250 µg bid	nr	nr	nr	nr
Szafranski et al, *Eur Respir J* 2003[24]	812 12 Bud 24% pla 26%	Bud 64 pla 65	Bud m 64% pla m 65%	1.27	cs Bud 36 pla 34	nr	nr	Argentina, Brazil, Denmark, Finland, Italy, Mexico, Poland, Portugal, South Africa, Spain, UK	Bud 1.01 L (37) pla 0.98 L (36)	Bud 200 µg bid	nr	nr	nr	nr
Calverley et al, *N Engl J Med* 2007[9]	6,112 36 FP 20% pla 22%	FP 65 pla 65	FP m 75 pla m 76	3.12	cs FP 43 pla 43	nr	mixed	Europe, Asia-Pacific, USA	FP pre bd 1.12±0.39 L (44.1) Post bd 1.22 ±0.41 L pla pre bd 1.12±0.40 L (44.1) Post bd 1.22 ±0.42 L	FP 500 µg bid	nr	nr	nr	Total, whole duration of the study FP 5.4% pla 5.1%

(*Continued*)

Table 1 (Continued).

Reference	Number of pts, length of ICS therapy (months), previous use of OCS and/or ICS	Mean age	Gender (%)	M/F ratio	% current and ex-smokers	Definition of former smokers	Ethnicity	Geographic area	Mean FEV_1 (pre-post bd) absolute value in liters (% predicted)	ICS and dosage	Baseline bone mass density	Vit D before	Vit D during	Bone fractures
Calverley et al, *Respir Res* 2008[30]	911 12 No in 6 weeks prior to study	MF-DPI 800 μg 65.3 MF-DPI 400 μg 65 pla 65	MF-DPI 800 μg m 69% MF-DPI 400 μg m 67% pla m 69%	2.15	cs 28.3	Quitting smoking ≥12 months before the study	MF-DPI 800 μg white 88% MF-DPI 400 μg white 86% pla white 85%	UK	MF 800 μg qd pm pre bd 1.32 L (43) Post bd 1.45 L (47) MF 400 μg bid pre bd 1.25 L (42) Post bd 1.38 L (469) pla pre bd 1.26 L (42.1) Post bd 1.41 L (47)	MF 800 μg qd pm 400 μg bid	nr	nr	nr	≤1% in groups
Shaker et al, *COPD* 2009[23]	254 24–48 No in 6 months prior to study	Bud 63.6 pla 63.6	Bud m 62 pla m 54	1,39	cs 100	nr	Ca	Denmark, Netherlands	Post bd Bud 1.53 L (51) pla 1.53 L (53)	Bud 400 μg bid	nr	nr	nr	nr
Lapperre et al, *Ann Intern Med* 2009[28]	114 30 No in 6 months prior to study	FP 6m 64 FP 30m 62 pla 59	FP 6m m 84.6 FP 30m m 88.4 pla 83.3	6.21	cs FP 30 months 61.5 FP 6 months 53.8 pla 70.8	nr	Nr	Netherlands	FP 30 months pre bd (57); post bd (64) FP 6 months pre bd (59); post bd (65) pla pre bd (54); post bd (61)	FP 500 μg bid for 30 months FP 500 μg bid for 6 months	nr	nr	nr	nr

(*Continued*)

Table 1 (Continued).

Reference	Number of pts, length of ICS therapy (months), previous use of OCS and/or ICS	Mean age	Gender (%)	M/F ratio	% current and ex-smokers	Definition of former smokers	Ethnicity	Geographic area	Mean FEV_1 (pre-post bd) absolute value in liters (% predicted)	ICS and dosage	Baseline bone mass density	Vit D before	Vit D during	Bone fractures
Tashkin et al, *Int J Chron Obstruct Pulmon Dis* 2012[31]	1,055 12 nr	MF400 60.2 pla 58.8	MF400 m 78% pla m 78%	3.22	cs MF 44; pla 46 es MF 56; pla 54	nr	ca: 71.9% as: 16.9% mr: 9.4%	Africa, Asia, Europe, North, Central, South America	MF 1.255 L pla 1.227 L	MF 400 μg bid	nr	nr	nr	MF 3 (radio, facial bone, rib) pla 1 (foot)
Doherty et al, *Int J Chron Obstruct Pulmon Dis* 2012[32]	1,196 12 No in previous 4 weeks	MF 60.5 pla 58.8	MF m 78 pla m 75	3.04	cs MF 53; pla 51 es MF 47; pla 49	≥10 pack/year history	MF white 70% pla white 66%	USA	MF post bd 40.2±11.7 pla post bd 38.5±11.5	MF 400 μg bid	nr	nr	nr	nr
Vestbo et al, *Lancet* 2016[35]	16,485 20 FF 33% pla 33%	FF 65 pla 65	FF m 74 pla m 75	3.92	cs FF 47 pla 47	nr	ca: 81% as: 17%	Africa, Asia, Australia, Europe, North, Central, South America	post bd FF 1.70 (59.6) pla 1.70 (59.7)	FF 92 μg qd	nr	nr	nr	FF 79 (2%) pla 78 (2%)

Abbreviations: as, Asian; bd, bronchodilator; BdP, beclomethasone dipropionate; bid, twice a day; Bud, budesonide; ca, Caucasian; cs, current smokers; DPI, dry powder inhaler; es, ex-smokers; f, females; FEV_1, forced expiratory volume in 1 s; FF, fluticasone furoate; FP, fluticasone propionate; ICS, inhaled corticosteroid; m, males; MF, mometasone furoate; mr, multiracial; nr, not reported; OCS, oral corticosteroid; pla, placebo; Pred, prednisolone; pm, evening; pt, patient; qd, once a day; RCT, randomized controlled trial; TA, triamcinolone acetonide; Vit, vitamin.

femur were significantly lower in the triamcinolone arm (P=0.007 and P<0.001, respectively).[34]

Incidence of bone fractures

Generally speaking, no differences were found between the numbers of bone fractures reported among patients receiving an ICS versus placebo. Pauwels et al found no significant differences in the development of new fractures with budesonide and placebo over a treatment period of 3 years (n=8 vs n=3; P=0.50) in 185 female and 468 male patients.[21] Similarly, in the TORCH study, the incidence of fractures was 5.4% in the fluticasone propionate arm and 5.1% in the placebo arm, and this difference was not significant.[9]

In the ISOLDE study, fractures were reported to have occurred in 4.6% of 370 patients receiving placebo and 2.4% of 372 patients receiving fluticasone propionate.[26] Calverley et al found that the incidence of bone fractures among patients treated with mometasone and placebo was lower than 1% each.[30] Tashkin et al also reported an incidence of fractures lower than 1% with both mometasone and placebo.[31] In the SUMMIT study, Vestbo et al reported 79 bone fractures with fluticasone furoate and 78 with placebo, amounting to an incidence of 2% in both groups.[35]

Discussion

Numerous factors contribute to decreased BMD and an increased likelihood of bone fractures in patients with COPD. First, the systemic chronic inflammation present in patients with stable COPD may have a direct local effect on bone homeostasis.[37] For example, the levels of inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α,[38] are increased in the blood of patients with stable COPD and may upregulate bone resorption by stimulating osteoclast development.[39] Hypogonadism is also relatively common in male patients with COPD,[40] and if untreated can reduce the anabolic stimulus on formation of bone, as well as weakening skeletal muscle and limiting physical activity.[41] Moreover, the bone resorption marker collagen type I β-isomerized C-terminal telopeptide increases significantly in patients with COPD during exacerbation (P<0.01 compared with stable patients and P<0.001 compared with healthy volunteers).[42] This indicates that COPD exacerbation may have detrimental effects on bone, and this is thought to be due to the intensification of characteristic disease symptoms such as inflammation, hypoxia, and oxidative stress during exacerbations.[42] Inhaled ICSs may also disrupt bone homeostasis and induce osteoporosis[6] by reducing osteoblastogenesis from bone marrow mesenchymal cells,[43] inducing osteoblast apoptosis by the production of reactive oxygen species,[44] and by the suppression of osteoclastogenesis.[45]

Two previous meta-analyses have highlighted an increased relative risk of bone fractures in COPD patients receiving long-term treatment with ICSs. The first was designed to study the dose–response relationship between ICS use and the bone fracture risk, but also included patients with asthma and studied non-vertebral fractures only. This analysis found an increased relative risk of bone fractures of 12% for each 1,000 μg (beclomethasone dipropionate equivalent) increase in daily ICS dose, though this result was not significant (95% confidence interval [CI] 1.00–1.26). Furthermore, this meta-analysis was limited by the involvement of only five case–control studies, two of which used the same databases, a lack of subgroup analysis, and substantial heterogeneity.[11]

The second meta-analysis by Loke et al was based on 16 RCTs and 7 observational studies.[10] Unlike the first, this analysis evaluated all types of bone fractures. The authors found that ICS exposure was significantly (P=0.04) associated with a relative increase of more than 20% in the likelihood of bone fractures in patients with COPD receiving ICSs in RCTs.[10] The number needed to harm was estimated to be 83 over a 3-year ICS treatment period based on the 5.1% bone fracture rates in the salmeterol and placebo arms of the TORCH trial.[36] Again, the authors of this analysis reported some limitations of their study, such as the use of data from unpublished, non-peer reviewed company reports. Moreover, most of the RCTs included did not use specific methods to define and report the bone fractures, and it is possible that misclassification or underdiagnosis occurred. The timing of fractures with relation to the use of ICSs was also not reported, and results may have been affected by the inclusion of patients who received ICSs before joining their trial and the receipt of oral glucocorticoids by some control group patients on study.

The statistical significance of the outcomes of these analyses is inconsistent and subject to a degree of uncertainty in that the established P-values and CIs lie close to the significance threshold in both cases (P=0.04, significant; 95% CI 1.00–1.26, non-significant).[10,11] The limitations associated with these analyses and their confounding results, along with the subsequent review on the topic by

the Cochrane Collaboration group based on a narrow scope of studies, highlight the need to further explore this potential relationship.

Some studies in the real life literature, however, provide conflicting results on the impact of ICSs on fracture risk. For example, a retrospective cohort study conducted using a large UK primary care database demonstrated that while users of inhaled ICSs have an increased risk of fracture, this excess risk may be associated with the underlying respiratory disease more than the medicines used to treat it.[46] Meanwhile, a large case–control study within the Dutch PHARMO-RLS database found that patients using inhaled ICSs did not have an increased risk of fracture after adjusting for underlying disease severity.[47]

We report the results of a narrative review of all published RCTs comparing long-term (at least 12 months) treatment with an ICS alone versus placebo in patients with stable COPD. Our aim was to study the potential association between treatment with ICSs and risk of bone fractures in patients with COPD in the relevant literature; however, none of the identified RCTs were specifically designed to measure the risk of bone fractures. This is reflected in the duration of the studies (12 months to 48 months), which was not calculated with the aim of observing bone-related endpoints in mind. Instead, these studies investigated mainly respiratory and mortality endpoints.

Overall, we found missing, incomplete, or contradictory data on changes in BMD and bone fractures in the identified studies. When data were collected on changes in BMD and fractures, they were reported in summary per treatment group and were not presented individually for males and females. Given the increased incidence of osteoporosis and increased fracture risk in postmenopausal women compared with men of a similar age,[48] and considering the general age of patients in the RCTs identified in our review, it would indeed be helpful if gender-specific data were reported for these outcomes.

With oral glucocorticoid therapy, increased fracture risk is frequently seen within the first three to six months.[49] However, data have been reported that suggest how patients taking oral glucocorticoid therapy may still have a greater risk of fracture compared with untreated patients with a similar BMD, as measured by dual X-ray absorptiometry.[50] Although inhaled ICSs and oral glucocorticoids are different, these data suggest that glucocorticoid-induced fracture risk may, in fact, be independent of BMD.[8]

Only a fraction of patients in each study had measurements of bone density, if any, and baseline bone density was rarely measured. As BMD is an important factor in bone strength, such measurements would be useful for the accurate correlation of COPD treatment via ICSs with bone weakening.[51]

A potential limitation of our review is that it focused solely on comparisons of ICS versus placebo and did not include any data from studies of ICS-/bronchodilator combinations. Dual therapies are recommended for the treatment of COPD rather than ICS monotherapy, and so inclusion of studies investigating dual therapy could have provided a wider pool of BMD data relevant to everyday practice. Owing to the inconsistent results obtained from previous literature reviews on the association between ICS use and fracture risk in patients with COPD and the potential effects of LAMAs or LABAs on bone metabolism, such studies were excluded from our review to facilitate a stricter focus on the potential effects of ICSs on bone metabolism as a means of investigating this relationship in more detail.

We found that information on the presence of bone fractures was reported in only a few of the RCTs identified. In addition, these studies lacked adequate information on the main risk factors that may affect BMD and/or bone fractures (Table 2). For example, tobacco smoking is an

Table 2 Main risk factors that may affect bone mineral density and/or the risk of bone fractures

Established:
Age
Gender
Ethnicity
Family history
Genes
Smoking
Vitamin D serum levels
Body composition
Physical activity
Menopause and hypogonadism
Comorbidities (diabetes mellitus)
Drugs (glucocorticoids, thiazide diuretics, statins, sex steroids, antidiabetic agents, acid-reducing drugs, selective serotonin reuptake inhibitors, heparin, beta 2 adrenergic
Systemic inflammation
Controversial:
Alcohol use
Tea use

Note: Data from references.[8,13–19,37,39–41,48–50,52–54,56–60]

important risk factor for osteoporosis, associated with increased rates of vertebral and hip fractures.[52–55] Yet, data comparing the risk of bone fractures between current smokers and former smokers are not reported. Likewise, the degree of baseline physical activity of the patients with COPD is not given; physical activity is a risk factor for osteoporosis and may also increase the risk of instability and falls, and, consequently, of bone fractures.[56] Discussion of the rates of bone fracture reported across the identified RCTs is also limited by the lack of a standardized definition of the term "bone fracture" and the provision of minimal information on fracture locations and impact across the studies.

Many of the reviewed studies also did not report data on important prior/concomitant therapies and supplements relevant to bone. For instance, data on the intake of oral and/or parenteral glucocorticoids, which are recommended for the treatment of moderate-to-severe COPD exacerbations and can influence osteoporosis,[2] prior to and during the study are not reported. Furthermore, no data on the intake of vitamin D supplements, with or without calcium, were provided.[9,21,26,30,31,35] The components of diet (such as alcohol consumption), duration of sun exposure, and comorbidities known to modulate the risk of osteoporosis, like diabetes mellitus, were also missing.[57–65]

In conclusion, the relationship between long-term ICS use and the risk of bone fractures in patients with stable COPD remains unclear, due to data deficiencies and the use of inconsistent terminology across the literature studied. However, the development of future RCTs specifically designed to study the association between ICSs and bone fractures would represent an important step toward fully elucidating the nature of this uncertain relationship. Such studies should consider the limitations of previous COPD studies reporting bone outcomes outlined in this review, including the need to capture important patient baseline information, such as gender, age, BMI, smoking status, and comorbidities, such as the presence of diabetes.

Abbreviation list

BMD, bone mineral density; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; IL, interleukin; LABA, long-acting β2-adrenergic agonist; LAMA, long-acting muscarinic antagonist; RCT, randomized controlled trial; TNF, tumor necrosis factor.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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