

The risk of osteoporosis in patients with asthma

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ABSTRACT

It is well-known that use of continuous systemic corticosteroids (SG) affects bone metabolism, bone mineral density (BMD), and ultimately increases the risk of osteoporosis. In patients with asthma, on the other hand, the effects of long-term high-dose inhaled corticosteroids (ICS) on BMD and risk of osteoporotic fractures is controversial. The reasons for this inconsistency could be explained by the fact that only few long-term studies investigating the effect of ICS in patients with asthma exist. The studies are characterized by different study designs and duration of ICS exposure, small study populations, and differences between the used ICS. The aim of this article is to unravel which factors, if any, that contribute to an increased risk of osteoporosis in patients with asthma and to summarize the evidence regarding adverse effects of ICS on bone metabolism, BMD and osteoporotic fractures in patients with asthma.

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Introduction

Asthma is a chronic inflammatory disease characterized by variable airflow obstruction and bronchial hyper-responsiveness [1]. Asthma causes significant morbidity that is associated with increased use of health-care services and decreased quality of life [2,3]. It affects both children and adults and it is estimated that approximately 300 million people worldwide have asthma [1,4]. The main symptoms are wheezing, shortness of breath, cough, and chest tightness that vary over time in occurrence, intensity and frequency [5,6]. Five to ten percent of all affected individuals have severe asthma defined as poor symptom control and frequent exacerbations despite maximal inhalation therapy [6–8]. Corticosteroids (CS) are the most effective anti-inflammatory medication for the treatment of persistent asthma and targeting CS to the airways (inhaled corticosteroids (ICS)) leads to fewer side effects than systemic corticosteroids (SC) [2,9]. Regular use of ICS reduces the need for SC [10].



There is, however, concern that long-term use of even moderate or high doses of ICS may be associated with systemic adverse effects such as reduced bone mineral density (BMD), fractures and osteoporosis [11,12]. This may decrease adherence to prescribed asthma medication

resulting in poor disease control, more visits to the emergency room, and increased disease-related health-care costs [13]. Systemic corticosteroids have been shown to increase the risk of fractures and osteoporosis [7,14]. Since high doses of ICS can suppress the *hypothalamic-pituitary-adrenal (HPA) axis* [15,16] and affect biochemical markers of bone turnover [15] one might speculate that use of moderate and high doses of ICS for longer periods of time can cause the same systemic adverse effects as SC.

The aim of this article is to review which factors that contribute to an increased risk of osteoporosis in patients with asthma, and to summarize the evidence regarding adverse effects of ICS on bone metabolism, BMD, and the risk of osteoporotic fractures [13].

Osteoporosis in general

Osteoporosis is the most common – yet often under-diagnosed – metabolic bone disease. It is estimated that approximately 200 million people worldwide suffer from osteoporosis [17]. Osteoporosis is a systemic bone disorder characterized by low bone mass and micro-architectural deterioration of bone tissue, which lead to reduced mechanical strength and

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Table 1. Table modified from Wilkins CH. Clin Interv Aging. 2007; 2(3): 389–394. Osteoporosis screening and risk management.

Risk factors for osteoporosis	
Nonmodifiable	Modifiable
Female sex	Smoking
Advanced age	Sedentary lifestyle
Low peak bone mass	Inadequate vitamin D intake or exposure to sun
Genetic susceptibility	Inadequate calcium intake
Personal history of fracture	Low body weight (BMI <19)
	Malnutrition
	Estrogen deficiency
	Hypogonadism
	Menopause before 45 year
	Chronic drug therapy (e.g. glucocorticoid)

increased risk of fracture. The strength of the bone depends on BMD and bone quality. The BMD is measured by the *dual-energy X-ray absorptiometry* (DXA) scan and is expressed as a T-score, the number of standard deviations (SDs) the measured BMD differs from BMD in healthy young individuals [18]. Osteoporosis is defined as low energy fracture in the spine or hip or a BMD T-score ≤ -2.5 at the lumbar spine or hip region [18]. Both hip- and vertebral fractures increase morbidity and mortality as the patient often becomes less mobile and in addition, each vertebral fracture is associated with a 9% decline in vital lung capacity [19,20]. The prevalence of osteoporosis in British patients with mild/moderate and severe asthma is 4% and 16%, respectively, and 3% among non-asthma controls [21]. Well-known risk factors for osteoporosis include female sex, advanced age, low body weight, early menopause, malnutrition, and genetic susceptibility (see also Table 1) [22–25]. Some of these risk factors are common for both osteoporosis and asthma.

Risk factors for osteoporosis in patients with asthma

Systemic inflammation

Studies have emphasized the role of the inflammatory response in chronic inflammatory airway diseases in the development of osteoporosis [26–28]. One of the pathways involved in the pathogenesis of osteoporosis is the *OPG/RANK/RANKL* axis [29]. Receptor-activator of nuclear factor kappa-B ligand (RANKL) is secreted by the osteocytes and osteoblasts and binds specifically to the receptor-activator of nuclear kappa-B (RANK) on osteoclast progenitors. The RANKL-RANK interaction increases *osteoclastogenesis* by promoting maturation of osteoclast progenitors into mature osteoclasts.

Osteoprotegerin (OPG) is produced in osteoblasts and bone stromal cells and has a similar structure as the RANK-receptor and act as a decoy receptor by binding and neutralizing RANKL thereby inhibiting *osteoclastogenesis*. In systemic inflammation, bone stromal cells and monocytes secrete cytokines like *Interleukin-1 β* (*IL-1 β*), *tumor necrosis factor (TNF)- α* , *IL-6*, and *IL-17*, which in turn increase the production of both RANKL and OPG, but with dominant effect on RANKL. These cytokines tilt the balance of the OPG/RANK/RANKL axis toward RANKL resulting in increased bone resorption and impaired bone strength [29,30].

In COPD (chronic obstructive pulmonary disease), osteoporosis is more common than in asthma, which is partly explained by the fact that patients with COPD have a higher systemic inflammatory response [8]. Although the inflammation in asthma is confined to the airway mucosa and there is little evidence of systemic inflammation in contrast to patients with COPD, secretion of pro-resorptive cytokines such as *TNF- α* and *IL-1 β* amplify the inflammatory response and may play a role in more severe disease [8].

Smoking

The prevalence of smoking among patients with asthma is similar to that of the general population [31]. Smoking weakens the skeletal muscle and reduces BMD, increases fracture risk, and prolongs bone healing. The risk of osteoporosis increases with higher cigarette consumption [27]. Smokers with asthma experience worse asthma control with accelerated decline in lung function and increased severity of air-flow obstruction compared to non-smoking asthmatic patients [32–34]. There also seems to be an association between asthma severity and smoke prevalence [35]. Mechanisms for the adverse effects of smoking in asthma include altered airway inflammation with a predominance of activated macrophages and neutrophils as in early COPD [32,33] and corticosteroid insensitivity [34]. Neutrophil numbers in airways are known to correlate to rate of decline in lung function [36] and as neutrophils are not normally responsive to corticosteroid treatment [32,33], persistent exposure to cigarette smoke in patients with asthma may necessitate the use of SG as acute and chronic add-on therapy [5].

Vitamin D deficiency

Vitamin D deficiency may increase the risk of both asthma and osteoporosis. Several cross-sectional

studies show that low serum levels of vitamin D in patients with asthma are associated with impaired lung function, higher exacerbation frequency, and reduced corticosteroid response [37]. In a meta-analysis, the prevalence of vitamin D deficiency defined as serum 25-hydroxyvitamin D (25(OH)D levels <20 ng/ml was 28.5% in children with asthma [38]. Di Rosa et al. found that vitamin D facilitates the expression of inflammatory mediators such as *IL-1 β* , *IL-6*, and *TNF- α* in human monocytes/macrophages [39]. In addition, *TNF- α* levels were increased in patients with asthma with acute asthma exacerbations and vitamin D deficiency compared to patients with acute exacerbations *without* deficiency suggesting that vitamin D deficiency may increase inflammation. Supplemental vitamin D increased the corticosteroid response in such patients [40]. Furthermore, in female patients with asthma and low vitamin D levels an accelerated decline in forced expiratory volume in 1 s (FEV₁) as well as decrease in BMD over time have been observed [41].

Low levels of vitamin D reduce intestinal absorption of calcium and subsequently plasma calcium, which in turn stimulates the parathyroid glands to increase secretion of parathyroid hormone (PTH) [42]. PTH stimulates immature osteoblastic cells to increase RANKL production, which in turn promotes *osteoclastogenesis*, increased bone resorption, and mobilization of calcium from the skeleton [42,43] but also a decrease in BMD. Finally, low levels of vitamin D are associated with muscle weakness and falling, which increases the risk of fractures [44].

Sedentary lifestyle

In a recently published study, children and adolescents undergoing regular asthma treatment had reduced functional capacity and sedentary behavior and there was a correlation between high *TNF- α* levels and low daily physical activity levels [45].

Physical inactivity results in muscle weakness, increased risk of falling, and reduction in mechanical loading on the bones [46] which may decrease BMD.

Pharmacodynamics of corticosteroids on bone

Corticosteroids in general affect most organs in the body. Of relevance for fracture risk and osteoporosis, glucocorticoids induce sarcopenia that decreases muscle strength and increases risk of falls. In addition, glucocorticoids increase renal excretion of calcium and decrease intestinal calcium absorption, which leads to a negative calcium balance and activation of

osteoclasts and bone resorption. Furthermore, the production of growth hormone and sex hormones is reduced which leads to decreased bone formation and increased bone resorption, respectively (Figure 1) [47]. In bone, glucocorticoids initially increase osteoclastogenesis and bone resorption, which subsequently, through coupling, increases osteoblastogenesis and bone formation. Therefore, the bone loss during short-term glucocorticoid treatment is only minimal. After longer-term treatment, however, glucocorticoids *decrease* osteoblastogenesis and bone formation [48].

The synthetic corticosteroids developed for inhalational therapy have a higher selectivity for the glucocorticoid receptor, a greater potency, and a low systemic bioavailability compared to orally administered compounds [49]. Their introduction constituted a major improvement in asthma treatment as they act locally in the lungs to reduce airway inflammation, prevent exacerbations, and dissolve many of the symptomatic manifestations of asthma [50,51] with fewer adverse effects than the orally administered glucocorticoids. ICS is still the cornerstone in treatment of patients with asthma since they are highly effective and often required for long-term control [52]. In patients with frequent exacerbations and in those with severe symptoms, higher doses of ICS as well as SG as intermittent or maintenance therapy will be needed [52].

Systemic glucocorticoids and bone

Glucocorticoid-induced bone loss is more marked at skeletal sites with a high trabecular content [53]. Due to the effects on bone cells described above, bone loss with oral corticosteroid therapy is time dependent and more rapid in the first 12–24 months [54]; however, the bone loss with short-course use of SG appears to be reversible [55]. Fracture risk increases markedly within 3 to 6 months after initiation of systemic corticosteroid therapy ≥ 5 mg of prednisolone (or equivalent) daily [56]. In addition, for any given BMD, fracture risk is increased in SG-users compared to non-users [57]. However, the maximum tolerable amount of SG given as separate short courses is unclear and probably individual [55]. Mori et al. assessed the effect on BMD, when SG (equivalent to average daily dose of 3.23 mg prednisolone) was given intermittently in patients with asthma for acute exacerbations during 1 year [58]. Serum N-terminal telopeptide (NTX), a bone resorption marker, was significantly higher in the SG group than in the group receiving ICS, but SG, however, had no effect on BMD. Pack et al. showed that patients with asthma receiving high-dose ICS (beclomethasone dipropionate, BDP, 1000–2000 μ g/day for an average

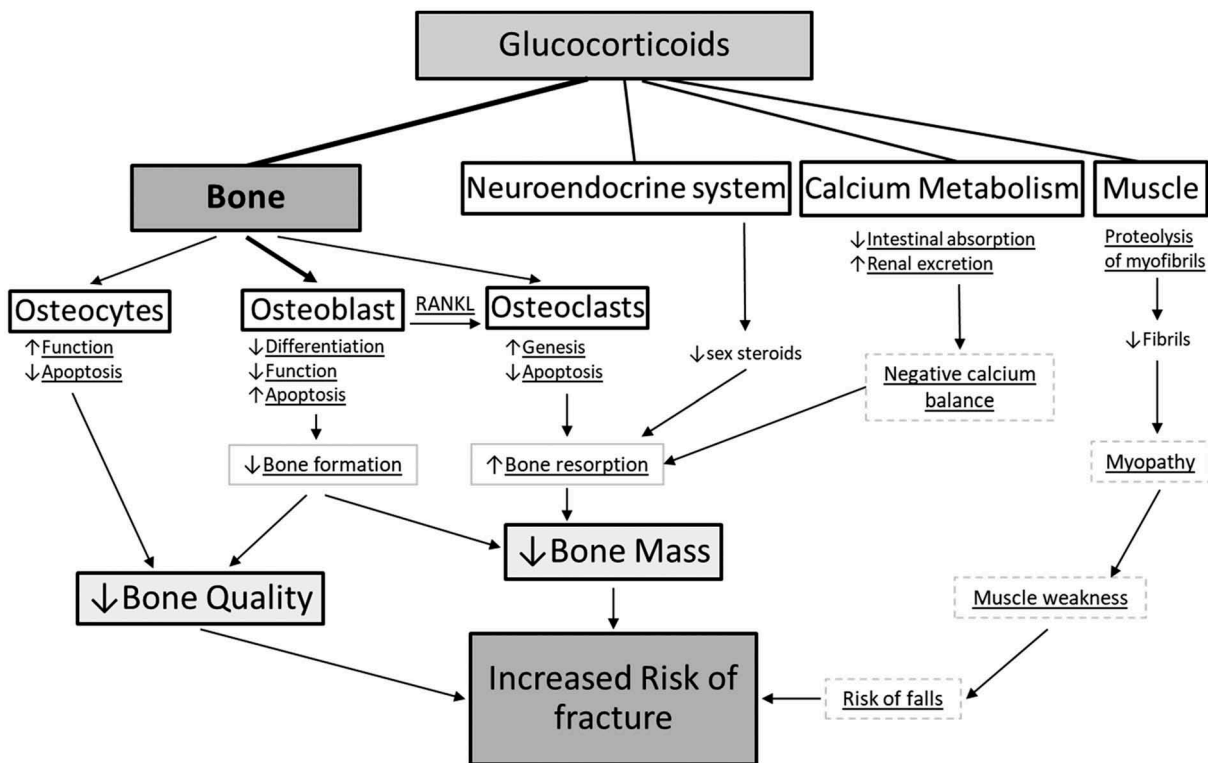


Figure 1. Shows the direct and indirect effects of glucocorticoids on bone leading to glucocorticoid-induced osteoporosis and fractures. Figure modified from Canalis et al. [46].

period of 3 years) as well as continuous or intermittent systemic corticosteroids had reduced BMD compared to patients with asthma not receiving any steroid treatment [59]. The frequency of previous short courses of SG, which may influence the results was, however, not described. In a 4-year longitudinal study [60], patients with asthma who only received sporadic short courses of systemic corticosteroid (i.e., < or = 2.5 courses per year) showed significantly less bone loss in the spine than those who received frequent short courses of systemic corticosteroid (i.e., >2.5 courses per year). Finally, Luengo et al. [61] did not find any difference in the rate of bone loss in patients with asthma receiving ICS (BDP or budesonide (BUD)) (mean dose, $662 \pm 278 \mu\text{g/d}$), irrespective of the use of sporadic short courses of oral corticosteroid (i.e. 1 to 6 courses per 2 years) in a case-control study [61].

In studies with healthy individuals and patients with multiple sclerosis, respectively, high dose, short-term intravenous glucocorticoid therapy (methylprednisolone, 15 mg/kg/day for 10 days) induced an immediate and marked decrease in bone formation markers although the bone formation markers subsequently returned to baseline [62,63]. Altogether, it appears that the intermittent sporadic use of SG is relatively safe with regard to bone loss.

Inhaled corticosteroids and bone

There are conflicting reports on whether, and to what extent, ICS affects bone metabolism and the risk of osteoporosis in patients with asthma. ICS have systemic activity due to absorption from the lungs and, to some extent, from the gastrointestinal tract [64]. Studies show that all ICS, and especially fluticasone at doses above $800 \mu\text{g/day}$, exhibit dose-related adrenal suppression and affects the endogenous cortisol production and bone metabolism although to a lesser extent than low-dose SG (5–7.5 mg prednisolone daily) [16,65,66]. So far, it is not evident that the observed hormonal and biochemical changes translate into clinically relevant changes in BMD or an increased fracture risk.

ICS and BMD/Osteoporosis

In a cross-sectional study conducted by Laatikainen et al., spinal and femoral neck BMD were assessed in asthmatic females ($n = 119$), aged 47–56 years, and compared to non-asthmatics ($n = 3103$) [67]. The patients with asthma were sub-categorized into 3 groups (no use of corticosteroids; ICS group with mean duration of treatment of 5.2 years and mean

daily dose of 0,8 mg BUD or 1,1 mg BDP, or oral corticosteroid). BMDs were lower in patients with asthma compared to non-asthmatics, although the difference was not statistically significant ($p > 0.05$) [67]. This association could be related to previous systemic corticosteroid treatments or to the disease itself (*confounding by indication*). Furthermore, spinal and femoral BMDs were not significantly different in patients with asthma and ICS treatment compared to the group of asthma patients who did not use corticosteroid. The duration of ICS treatment and duration of regular SG treatment, however, correlated negatively with spinal BMD [67]. Fujita et al. assessed BMD and bone turnover markers in pre- and postmenopausal women with asthma ($n = 36$), aged 40–60, treated with or without ICS (BDP) compared to healthy controls (pre- and postmenopausal women, $n = 45$) [68]. They found that use of ICS was only associated with reduced BMD in early postmenopausal women with asthma ($p < 0.05$) (dose of BDP $534 \pm 316 \mu\text{g}/\text{day}$) and that there was a corresponding reduction in the levels of the bone formation marker osteocalcin [68]. The reason for this association could be that, when bone formation is inhibited by corticosteroids, the women are more vulnerable to a high turnover condition like early menopause. Wong et al. [69] showed in a cross-sectional survey that cumulative dose of ICS (80% of patients taking BDP, median dose was 876 mg) was negatively associated with BMD ($p < 0.05$) in 196 patients with asthma aged 20–40 years. The duration of use of ICS ranged from 0.5 to 24 years (a median of 6 years). In another cross-sectional study Sivri et al. also showed a significantly lower BMD at both the hip and spine in female patients with asthma ($n = 32$, both pre- and postmenopausal) exposed to regular use of ICS (BDP 750–1500 $\mu\text{g}/\text{day}$ for at least 3 months) [53]. A significant negative correlation ($p < 0.05$) was seen between the duration of asthma, duration of corticosteroid use, the mean daily, and the cumulative dose of corticosteroids and spine BMD [53]. In a small study, Tug T. et al. assessed BMD in patients with asthma ($n = 18$, mostly females) treated with long-term ICS (BUD at least 800 $\mu\text{g}/\text{day}$ from 3 months up to more than 24 months) compared with healthy controls and found no difference in BMD between the two groups ($p > 0.05$) [70]. Oh J. et al. compared the prevalence of osteoporosis in patients with asthma, ACO (asthma-COPD overlap) and COPD in a retrospective, cross-sectional study ($n = 321$). All patients were treated with ICS and/or other bronchodilators (either fluticasone/salmeterol, BUD/formoterol or tiotropium). The use of ICS was not associated with prevalence of osteoporosis in patients with asthma ($p > 0.05$) and osteoporosis

tended to be more prevalent in patients with ACO than in those with asthma [71]. Conclusively, cross-sectional and short-term studies seem to have conflicting results regarding the effect of ICS on BMD. This may be due to small study populations; potential differences between the available ICS used (without sufficient data available to assign precise dose equivalents for the systemic adverse effects); different age groups; sex including menstrual status and uncertainty about the degree of earlier frequent treatment with SG use or co-administration with SG. In addition, the negative correlation between the duration of ICS treatment and BMD seen in some studies may be related to disease severity and not necessarily to the effect of ICS (*confounding by indication*).

In contrast to the short-term studies mentioned above, a 4-year longitudinal study without a control group, conducted by Matsumoto et al. [60] did not show a negative correlation between ICS and BMD. Matsumoto et al. assessed the lumbar BMD in men ($n = 15$) and postmenopausal women ($n = 20$) with asthma receiving daily dose of ICS (BDP, 765 $\mu\text{g} - \pm 389 \mu\text{g}$) and short courses of oral corticosteroids. Daily use of ICS was not associated with any changes in BMD ($p > 0.05$) [60]. Furthermore, no significant difference was found in change in BMD between the low-dose (i.e., $\leq 1,000 \mu\text{g}/\text{day}$) and high-dose (i.e., $> 1,000 \mu\text{g}/\text{day}$) BDP groups ($p > 0.05$). In Table 2 the included studies on ICS and BMD/Osteoporosis are summarized.

ICS and fracture risk

A cohort study ($n = 1671$) conducted by Hubbard T. et al. found a dose–response relationship between ICS and the risk of fracture that was independent of incident and historical exposure to oral corticosteroids ($p < 0.05$), specific type of airflow obstruction diagnosis (asthma, COPD and ACO patients were included), and use of bronchodilators (beclomethasone dipropionate, budesonide and fluticasone were regarded equipotent) [72]. In an epidemiological study, Melton et al. [73] found a 70% increase in overall fracture risk among unselected community patients with adult onset asthma ($n = 226$). The increased risk was primarily confined to individuals who also had COPD and was influenced by substantial ICS and SG corticosteroid use (hazard ratio, 1.7; 95% CI, 1.5 to 2.1). In the multivariate analysis, use of ICS among patients with asthma was not associated with fracture risk after adjustment for age [66]. In a meta-analysis, Loke et al. found that ICS use > 12 months in adults and children with asthma was not significantly associated with harmful effects on

Table 2. Characteristics of included studies on ICS and BMD/osteoporosis.

Study	Design	Glucocorticoid dosage	Type of ICS	Asthma patients	Controls	Outcome
Laatikainen AK, et al.	Cross-sectional	BUD 800 ± 200; BDP 1100 ± 500 (µg/day); or oral.	BUD or BDP (N = 72)	N = 119	N = 3103	BMD were lower in patients with asthma compared to non-asthmatics, however, the difference was not significant (p > 0.05)
Fujita K, et al.	Cohort	BDP 534 ± 316 (µg/day)	BDP	N = 36	N = 45	BMD were significantly lower in post-menopausal asthmatics patients (p < 0.05) but not in premenopausal compared to healthy controls (p < 0.05)
Wong CA, et al.	Cross-sectional	Median cumulative dose (BUD; BDP; FP) 876 mg (0.5–24 years)	BUD; BDP; FP	N = 196	N = 0	BMD was negatively associated with cumulative dose of ICS (p < 0.05)
Sivri A, et al.	Cross-sectional	BDP 750–1500 (µg/day)	BDP	N = 32	N = 26	BMD was significantly decreased in asthmatic patients compared to healthy controls (p < 0.05)
Tug T, et al.	Cohort	BUD > 800 (µg/day)	BUD	N = 18	N = 14	BMD was not significantly different between asthmatic patients and healthy controls (p > 0.05)
Oh JY, et al.	Cross-sectional	Unknown	Fluticasone/salmeterol; BUD/formoterol	N = 138	N = 0	Prevalence of osteoporosis and BMD was not associated with ICS use in asthmatic patients (p > 0.05)
Matsumoto H, et al.	Cohort	BDP 765 ± 389 (µg/day)	BDP	N = 35	N = 0	Daily use of ICS was not associated with changes in BMD. No significant difference was found in change in BMD between the low-dose and high-dose BDP groups (p > 0.05)

Abbreviations: budesonide (BUD), beclomethasone dipropionate (BDP), fluticasone propionate (FP).

fractures [1]. In a case-control study, Vestergaard P. et al. [14,74] found no increase in the risk of hip, spine, or forearm fractures in ICS users (n = 11,536) except at daily dosages above 1875 µg of budesonide or beclomethasone (equivalent to 7.5 mg prednisolone) (odds ratio 1.17 (1.00–1.38) [14]. Etminan et al. [75] conducted a meta-analysis (including six case-control studies, three cohort studies, and four randomized-controlled trials, RCT) and found no association between the use of ICS (duration-span from 1 month up to 8 years follow-up) and fractures in older adults. A slight increase in risk was, however, seen in those using high-dose ICS (> or = 700 µg per day BDP [76]; > BDP equivalent of >1,500 µg per day [77]). Etminan and coworkers included five studies, where the study population were only patients with COPD and further more smoking may be a potential confounder, which was not controlled for in most of the studies. The results from Etminan et al., differ slightly from the results from a previous meta-analysis by Loke et al. [78], who found a significant dose-related increase in

risk of fracture in ICS users with COPD [78]. The differences can be explained by the fact that patients with COPD have other characteristics and/or comorbidities such as increased systemic inflammation [8], higher prevalence of smoking [79], malnutrition and cachexia [20] and physical inactivity [46] which all may affect BMD and risk of fracture [24]. Furthermore, patients with asthma tend to be younger than patients with COPD [14], and finally, the severity of the disease itself can be the reason for the increased risk [80]. In Table 3 the included studies on ICS and fracture risk are summarized.

Conclusion

In patients with asthma, continuous low dose and frequent intermittent high-dose SG treatment affects BMD and hence increases the risk of osteoporosis, whereas sporadic short courses of SG treatment seem to be relatively safe. The current data regarding intermittent high-dose treatment with SG are, however,

Table 3. Characteristics of included studies on ICS and fracture risk.

Study	Design	Glucocorticoid dosage	Type of ICS	Asthma Patients	Controls	Outcome
Hubbard T et al.	Cohort study	Mean daily dose > 601 µg during a mean follow-up period of 9.4 years	BUD; BDP; FP	N = 774 (N = 468 exposed to ICS)	N = 0	Use of ICS was associated with dose-related increase in fracture risk independent of actual or previous exposure to SG (p < 0.05)
Melton et al.	Cohort study	Median cumulative corticoid dose of 1775 mg during a follow up period of median 18.8 years (258 µg/day)	Unknown	N = 226	N = 0	Use of ICS and SG was associated with a 70% increase in overall fracture risk, however this was primarily confined to asthma patients with concomitant COPD and with substantial use of SG (Hazard ratio: 1.7; 95% CI, 1.5 to 2.1)
Vestergaard P et al.	Case-control study	<1875 (µg/day)	BUD; BDP;	N = 4114	N = 8601	Use of ICS did not increase the risk of hip, spine or forearm fractures except at daily dosages above 1875 µg of BUD or BDP (odds ratio 1.17 (1.00–1.38))

Abbreviations: budesonide (BUD), beclomethasone dipropionate (BDP), fluticasone propionate (FP).

limited in patients with asthma. ICS treatment may have a dose-dependent effect on bone metabolism and subsequently risk of fracture. There are, however, inconsistencies in the results from studies concerning potential harmful effects of ICS treatment in the form of reduced BMD and increased risk of fracture.

Patients with severe asthma, ACO and/or co-administration of SG may have a slightly higher risk of osteoporotic fractures, and the prevalence of osteoporosis in patients with severe asthma and ACO is also higher compared to healthy controls. This might be due to smoking, sedentary lifestyle, a higher systemic inflammation, and the need of frequent intermittent or continuous SG or high-dose ICS.

ICS are highly effective drugs in patients with asthma and it is important to control local inflammation and disease activity to reduce the need for frequent oral corticosteroids. Patients should, however, be advised to use the lowest effective dose that adequately controls their asthma. More knowledge about the safety of high-dose ICS is needed, but based on the existing evidence, the effect of ICS seems to outweigh the risk. Furthermore, the overall risk of osteoporosis should be assessed in each patient, especially in patients with severe asthma or ACO in terms of timely diagnosis and prophylactic treatment.

Disclosure statement

No conflict of interest was declared.

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