The risk of osteoporosis in patients with asthma

Kumarathas, Indumathi; Harsløf, Torben; Andersen, Charlotte Uggerhøj; Langdahl, Bente; Hilberg, Ole; Bjørmer, Leif; Løkke, Anders

Published in:
European Clinical Respiratory Journal

DOI:
10.1080/20018525.2020.1763612

Publication date:
2020

Document version
Final published version

Document license
CC BY-NC

Citation for published version (APA):
Kumarathas, I., Harsløf, T., Andersen, C. U., Langdahl, B., Hilberg, O., Bjørmer, L., & Løkke, A. (2020). The risk of osteoporosis in patients with asthma. European Clinical Respiratory Journal, 7(1), [1763612].
https://doi.org/10.1080/20018525.2020.1763612

Terms of use
This work is brought to you by the University of Southern Denmark through the SDU Research Portal. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:
- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying this open access version.

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk
The risk of osteoporosis in patients with asthma

Indumathi Kumarathas, Torben Harssløf, Charlotte Uggerhøj Andersen, Bente Langdahl, Ole Hilberg, Leif Bjermer & Anders Løkke

To cite this article: Indumathi Kumarathas, Torben Harssløf, Charlotte Uggerhøj Andersen, Bente Langdahl, Ole Hilberg, Leif Bjermer & Anders Løkke (2020) The risk of osteoporosis in patients with asthma, European Clinical Respiratory Journal, 7:1, 1763612, DOI: 10.1080/20018525.2020.1763612

To link to this article: https://doi.org/10.1080/20018525.2020.1763612

© 2020 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

Published online: 19 May 2020.

Submit your article to this journal

Article views: 77

View related articles

View Crossmark data
The risk of osteoporosis in patients with asthma

Indumathi Kumarathas, Torben Harsløf, Charlotte Uggerhøj Andersen, Bente Langdahl, Ole Hilberg, Leif Bjermer and Anders Løkke

Department of Clinical Medicine, Steno Diabetes Center Aarhus, Aarhus, Denmark; Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark; Institute for Biomedicine, Aarhus University, Aarhus, Denmark; Department of Medicine, Vejle Hospital, Vejle, Denmark; Department of Respiratory Medicine and Allergology, Skaane University Hospital, Lund, Sweden

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.

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...
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-1β (IL-1β), 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-1β 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 airflow 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-1β, 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 osteoblastogenesis, 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 osteoblastogenesis 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 µg/day for an average
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 ± 278 µg/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 µg/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

---

*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].*
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 ± 316 µg/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 µg/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 µg/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 µg – ± 389 µg) 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., ≤1,000 µg/day) and high-dose (i.e., >1,000 µg/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
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,
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.

**ORCID**

Indumathi Kumarathas [http://orcid.org/0000-0001-9029-1064](http://orcid.org/0000-0001-9029-1064)

**References**

[1]. Loke YK, Gilbert D, Thavarajah M, et al. Bone mineral density and fracture risk with long-term use of inhaled corticosteroids in patients with asthma: systematic review and meta-analysis. BMJ Open. 2015;5(11): e008554.

[2]. Yanik B, Ayrim A, Ozol D, et al. Influence of obesity on bone mineral density in postmenopausal asthma patients undergoing treatment with inhaled corticosteroids. Clinics. 2009;64(4):313–318.

[3]. Gershon AS, Guan J, Wang C, et al. Describing and quantifying asthma comorbidity: a population study. PLoS One. 2012;7(5):e34967.

[4]. Masoli M, Fabian D, Holt S, et al. The global burden of asthma: executive summary of the GINA dissemination committee report. Allergy. 2004;59(5):469–478.

[5]. [https://ginasthma.org/wp-content/uploads/2016/05/WMS-GINA-2016-main-Pocket-Guide.pdf](https://ginasthma.org/wp-content/uploads/2016/05/WMS-GINA-2016-main-Pocket-Guide.pdf). 2016.

[6]. [https://www.who.int/respiratory/asthma/en/](https://www.who.int/respiratory/asthma/en/). 2019.

[7]. Daugherty J, Lin X, Baxter R, et al. The impact of long-term systemic glucocorticoid use in severe asthma: a UK retrospective cohort analysis. J Asthma. 2018;55 (6):651–658.

[8]. Barnes PJ. Cellular and molecular mechanisms of asthma and COPD. Clin Sci (Lond). 2017;131 (13):1541–1558.

[9]. Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. Report of a workshop held in

---

**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; FP       | 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).
I. KUMARATHAS ET AL.

Eze, France, October 1992. Am Rev Respir Dis. 1993;148(4 Pt 2):S1–26.

[10]. Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma. Respir Med. 2006;100(8):1307–1317.

[11]. Baylink DJ, Wergedal JE. Bone formation by osteocytes. Am J Physiol. 1971;221(3):669–678.

[12]. Rossi GA, Cerasoli F, Cazzola M. Safety of inhaled corticosteroids: room for improvement. Pulm Pharmacol Ther. 2007;20(1):23–35.

[13]. Heffler E, Madeira LNG, Ferrando M, et al. Inhaled corticosteroids safety and adverse effects in patients with asthma. J Allergy Clin Immunol Pract. 2018;6(3):776–781.

[14]. Vestergaard P, Rejnmark L, Moskilde L. Fracture risk associated with systemic and topical corticosteroids. J Intern Med. 2005;257(4):374–384.

[15]. Ebeling PR, Erbas B, Hopper JL, et al. Bone formation by osteocytes. J Bone Miner Res. 1998;13(8):1283–1289.

[16]. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. Arch Intern Med. 1999;159(9):941–955.

[17]. Sozen T, Ozisik L, Basaran NC. An overview and management of osteoporosis. Eur J Rheumatol. 2017;4(1):46–56.

[18]. Society DE. http://www.endocrinology.dk/index.php/3-calcium-og-knoglemetaboliske-sygdomme/3-osteoporose. 2017.

[19]. Langhammer A. Long-term therapy in COPD: any evidence of adverse effect on bone? Int J Chron Obstruct Pulmon Dis. 2009;4:365–380.

[20]. Inoue D, Watanabe R, Okazaki R. COPD and osteoporosis: links, risks, and treatment challenges. Int J Chron Obstruct Pulmon Dis. 2016;11:637–648.

[21]. Sweeney J, Patterson CC, Menzies-Gow A, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the optimum patient care research database and the British thoracic difficult asthma registry. Thorax. 2016;71(4):339–346.

[22]. Sambrook P, Cooper C. Osteoporosis. Lancet. 2006;367(9527):2010–2018.

[23]. Abe E, Sun L, Mechanick J, et al. Bone loss in thyroid disease: role of low TSH and high thyroid hormone. Ann N Y Acad Sci. 2007;1116(1):383–391.

[24]. Compston JE. Risk factors for osteoporosis. Clin Endocrinol (Oxf). 1992;36(3):223–224.

[25]. Wilkins CH. Osteoporosis screening and risk management. Clin Interv Aging. 2007;2(3):389–394.

[26]. Jorres RA, Welte T, Bals R, et al. Systematic manifestations and comorbidities in patients with chronic obstructive pulmonary disease (COPD) and their effect on clinical state and course of the disease—an overview of the cohort study COSYCONET. Dtsch Med Wochenshr. 2010;135(10):446–449.

[27]. Omoigui S. The Interleukin-6 inflammation pathway from cholesterol to aging – role of statins, bisphosphonates and plant polyphenols in aging and age-related diseases. Immun Ageing. 2007;4(1):1.

[28]. Katsura H, Kida K. A comparison of bone mineral density in elderly female patients with COPD and bronchial asthma. Chest. 2002;122(6):1949–1955.

[29]. Sarkar M, Bharadwaj R, Madabhavi I, et al. Osteoporosis in chronic obstructive pulmonary disease. Clin Med Insights Circ Respir Pulm Med. 2015;9:5–21.

[30]. Theoleyre S, Wittrant Y, Tat SK, et al. The molecular triad OPG/RANK/RANKL: involvement in the orchestration of pathophysiological bone remodeling. Cytokine Growth Factor Rev. 2004;15(6):457–475.

[31]. Jimenez-Ruiz CA, Andreas S, Lewis KE, et al. Statement on smoking cessation in COPD and other pulmonary diseases and in smokers with comorbidities who find it difficult to quit. Eur Respir J. 2015;46(1):61–79.

[32]. Boulet L-P, Catherine L, Francine A, et al. Smoking and asthma: clinical and radiologic features, lung function, and airway inflammation. Chest. 2006;129(3):661–668.

[33]. Chalmers GW, MacLeod KJ, Thomson L, et al. Smoking and airway inflammation in patients with mild asthma. Chest. 2001;120(6):1917–1922.

[34]. Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. Eur Respir J. 2013;41(3):716–726.

[35]. Strine TW, Balluz LS, Ford ES. The associations between smoking, physical inactivity, obesity, and asthma severity in the general US population. J Asthma. 2007;44(8):651–658.

[36]. Stanescu D, Sanna A, Veriter C, et al. Airways obstruction, chronic expectoration, and rapid decline of FEV1 in smokers are associated with increased levels of sputum neutrophils. Thorax. 1996;51(3):267–271.

[37]. Cassim R, Russell MA, Lodge CJ, et al. The role of circulating 25 hydroxyvitamin D in asthma: a systematic review. Allergy. 2015;70(4):339–354.

[38]. Jat KR, Khairwa A. Vitamin D and asthma in children: a systematic review and meta-analysis of observational studies. Lung India. 2017;34(4):355–363.

[39]. Di Rosa M, Malaguarnera G, De Gregorio C, et al. Immuno-modulatory effects of vitamin D3 in human monocyte and macrophages. Cell Immunol. 2012;280(1):36–43.

[40]. Lan N, Luo GY, Yang QX, et al. 25-Hydroxyvitamin D3-deficiency enhances oxidative stress and corticosteroid resistance in severe asthma exacerbation. Plos One. 2014;9(11):11.

[41]. Sposato B, Scalese M, Petruzzelli L, et al. Could a vitamin D deficiency cause a combined long-term FEV1 and bone mineral density deterioration in female asthmatics? Clin Ter. 2017;168(6):E388–E91.

[42]. Janssens W, Mathieu C, Boonen S, et al. Vitamin D deficiency and chronic obstructive pulmonary disease: a vicious circle. Vitam Horm. 2011;86:379–399.

[43]. Suda T, Takahashi N, Udagawa N, et al. Modulation of osteoclast differentiation and function by the new members of the tumor necrosis factor receptor and ligand families. Endocr Rev. 1999;20(3):345–357.

[44]. Kokturk N, Baha A, Oh Y-M, et al. Vitamin D deficiency: what does it mean for chronic obstructive pulmonary disease (COPD)? a comprehensive review for pulmonologists. Clin Respir J. 2018;12(2):382–397.

[45]. MM R. Patients with asthma have reduced functional capacity and sedentary behavior. J Pediatr (Rio J). 2018;96(1):53–59.
[46]. Cielen N, Maes K, Gayan-Ramirez G. Musculoskeletal disorders in chronic obstructive pulmonary disease. Biomed Res Int. 2014;2014:965764.

[47]. Canalis E, Mazzotti G, Giustina A, et al. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int. 2007;18(10):1319–1328.

[48]. Compton J. Management of glucocorticoid-induced osteoporosis. Nat Rev Rheumatol. 2010;6(2):82–88.

[49]. Osteoporos Int. 2001;12(9):853–859.

[50]. Durrani SR, Viswanathan RK, Busse WW. What effect does asthma treatment have on airway remodeling? Current perspectives. J Allergy Clin Immun. 2011;128(3):439–448.

[51]. Buehring B, Viswanathan R, Binkley N, et al. Glucocorticoid-induced osteoporosis: an update on effects and management. J Allergy Clin Immunol. 2013;132(5):1019–1030.

[52]. https://ginaasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-tracked_v1-3.pdf. 2018.

[53]. Sivri A, Coplu E. Effect of the long-term use of inhaled corticosteroids on bone mineral density in asthmatic women. Respirology. 2001;6(2):131–134.

[54]. Sambrook P, Birmingham J, Kempler S, et al. Corticosteroid effects on proximal femur bone loss. J Bone Miner Res. 1990;5(12):1211–1216.

[55]. Oh JY, Lee YS, Min KH, et al. Osteoporosis in Patients with Asthma–Chronic Obstructive Pulmonary Disease Overlap Syndrome. Tuberc Respir Dis (Seoul). 2018;81(1):73–79.

[56]. Hubbard R, Tattersfield A, Smith C, et al. Use of inhaled corticosteroids and the risk of fracture. Chest. 2006;130(4):1082–1088.

[57]. Luengo M, Del Rio L, Pons F, et al. Bone mineral density in asthmatic patients taking high dose inhaled flunisolide and fluticasone propionate in adult asthma patients. Ann Allergy Asthma Immunol. 2001;87(5):379–385.

[58]. Fujita K, Kasayama S, Hashimoto J, et al. Inhaled corticosteroids reduce bone mineral density in early post-menopausal but not premenopausal asthmatic women. J Bone Miner Res. 2001;16(4):782–787.

[59]. Wong CA, Walsh LJ, Smith CJ, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. Lancet. 2000;355(9213):1399–1403.

[60]. Packe GE, Douglas JG, Mcdonald AF, et al. Bone formation and transient increase of bone resorption in the course of high-dose, short-term glucocorticoid therapy in young patients with multiple sclerosis. J Clin Endocrinol Metab. 2004;89(10):4923–4928.

[61]. Godschalk MF, Downs RW. Effect of short-term glucocorticoids on serum osteocalcin in healthy young men. J Bone Miner Res. 1988;3(1):113–115.

[62]. Lee TA, Weiss KB. Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004;169(7):855–859.

[63]. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax. 2011;66(8):699–708.

[64]. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. Am J Respir Crit Care Med. 1998;157(3):S1–53.

[65]. Jennings BH, Andersson KE, Johansson SA. Assessment of systemic effects of inhaled glucocorticosteroids: comparison of the effects of inhaled budesonide and oral prednisolone on adrenal function and markers of bone turnover. Eur J Clin Pharmacol. 1991;40(1):77–82.

[66]. Casale TB, Nelson HS, Stricker WE, et al. Suppression of hypothalamic-pituitary-adrenal axis activity with inhaled flunisolide and fluticasone propionate in adult asthma patients. Ann Allergy Asthma Immunol. 2001;87(5):379–385.

[67]. Laatikainen AK, Kroger HP, Tukiainen HO, et al. Bone mineral density in perimenopausal women with asthma: a population-based cross-sectional study. Am J Respir Crit Care Med. 1999;159(4):1179–1185.

[68]. Fujita K, Kasayama S, Hashimoto J, et al. Inhaled corticosteroids reduce bone mineral density in early postmenopausal but not premenopausal asthmatic women. J Bone Miner Res. 2001;16(4):782–787.

[69]. Wong CA, Walsh LJ, Smith CJ, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. Lancet. 2000;355(9213):1399–1403.

[70]. Tug T, Kamanli A, Tug E. Effects of long-term inhaled steroid use on bone mineral density in asthma patients. J Investig Allergol Clin Immunol. 2001;11(4):300–302.

[71]. Oh JY, Lee YS, Min KH, et al. Osteoporosis in Patients with Asthma–Chronic Obstructive Pulmonary Disease Overlap Syndrome. Tuberc Respir Dis (Seoul). 2018;81(1):73–79.

[72]. Hubbard R, Tattersfield A, Smith C, et al. Use of inhaled corticosteroids and the risk of fracture. Chest. 2006;130(4):1082–1088.

[73]. Melton LJ 3rd, Patel A, Achenbach SJ, et al. Long-term fracture risk following adult-onset asthma: a population-based study. Osteoporos Int. 2004;15(4):311–316.

[74]. Vestergaard P, Rejmkark M, Mosekilde L. Fracture risk in patients with chronic lung diseases treated with bronchodilator drugs and inhaled and oral corticosteroids. Chest. 2007;132(5):1599–1607.

[75]. Etminan M, Sadatsafavi M, Ganjizadeh Zavareh S, et al. Inhaled corticosteroids and the risk of fractures in older adults: a systematic review and meta-analysis. Drug Saf. 2008;31(5):409–414.

[76]. Lee TA, Weiss KB. Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004;169(7):855–859.

[77]. Suissa S, Baltzan M, Kremer R, et al. Inhaled and nasal corticosteroid use and the risk of fracture. Am J Respir Crit Care Med. 2004;169(1):83–88.

[78]. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax. 2011;66(8):699–708.

[79]. Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. BMJ. 1997;315(7112):841–846.