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ASSOCIATION BETWEEN INHALED CORTICOSTEROIDS AND OSTEOPOROSIS: A REVIEW

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Abstract

Inhaled corticosteroids (ICS) are commonly prescribed to manage asthma and chronic obstructive pulmonary disease (COPD) due to their local anti-inflammatory effects in the airways. However, prolonged or high-dose ICS use has been associated with systemic adverse effects, including decreased bone mineral density (BMD) and increased risk of osteoporosis. This review aimed to examine the association between ICS use and the risk of osteoporosis or fractures, and to identify modifying factors such as dose, duration, patient age, sex, and type of corticosteroid used. Literature review was conducted using databases including PubMed, Scopus, and Web of Science. Articles were selected using specific inclusion and exclusion criteria. The review focused on original studies published up to March 2025, resulting in 28 relevant articles, of which 6–8 high-quality studies were analyzed in depth. Most studies demonstrated that long-term or high-dose ICS use is associated with decreased BMD and increased risk of fractures, especially in elderly COPD patients. The greatest risk was linked to fluticasone and budesonide at doses ≥500 µg/day. Some studies found neutral or even protective effects in specific subgroups, indicating population-dependent variability. Meta-analyses revealed conflicting results due to heterogeneity in populations and methodologies. High-dose and long-term ICS use may increase the risk of osteoporosis. Clinicians should consider individualized risk assessments and adopt strategies such as using the lowest effective dose, monitoring BMD, and providing calcium and vitamin D supplementation in at-risk populations.

Keywords: asthma; bone mineral density; fracture; inhaled corticosteroids; osteoporosis

1. INTRODUCTION

Inhaled corticosteroids (ICS) are the cornerstone therapy for managing chronic airway diseases such as asthma and chronic obstructive pulmonary disease (COPD), working by suppressing inflammation through immune-modulating mechanisms in the airways(Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2023). The local delivery of ICS allows for reduced systemic exposure compared to oral or parenteral corticosteroids, which makes them preferable in long-term treatment. ICS have been shown to reduce exacerbation

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frequency and improve quality of life in patients with chronic respiratory disease(Global Initiative for Asthma (GINA), 2025). However, accumulating evidence has raised concerns over the systemic adverse effects of ICS, especially when used at high doses or for prolonged durations, including the potential risk of reduced bone mineral density and osteoporosis(Patel, Naqvi, Griffiths, & Bloom, 2020).

One of the most well-recognized systemic effects of corticosteroids is glucocorticoid-induced osteoporosis (GIOP), which represents the most common form of secondary osteoporosis in clinical practice(Kobza, Herman, Papaioannou, Lau, & Adachi, 2021). Corticosteroids exert adverse effects on bone by inhibiting osteoblast activity, enhancing osteoclast-mediated bone resorption, and reducing calcium absorption in the intestines (Bhattarai, Shrestha, Rokka, & Shakya, 2020). These effects contribute to a decline in bone mineral density (BMD) and an increased risk of fractures over time.

Although systemic corticosteroids are widely known to have deleterious effects on bone, ICS have also been implicated in this risk through systemic absorption, particularly in high-potency formulations such as fluticasone and when delivered via devices with high lung deposition efficiency (Melani, Croce, Fabbri, Messina, & Bargagli, 2024). A growing number of observational and cohort studies have explored the association between ICS use and bone-related outcomes, but findings remain inconsistent. Some studies report a significant reduction in BMD and increased fracture incidence among long-term or high-dose ICS users(Gonzalez, Coulombe, Ernst, & Suissa, 2018),(Janson et al., 2021),(Peng et al., 2023). Additionally, recent local and international studies have proposed mechanisms involving gastrointestinal absorption of ICS and disruption of vitamin D metabolism as potential contributors to skeletal risks(Azzahra, Yohanes, & Sumiwi, 2023),(Zhang, Fan, Zhang, Xu, & Li, 2023).

Moreover, a matched cohort study by Price et al. (2019) demonstrated that high-dose ICS use was associated with a dose-dependent increase in the risk of developing osteoporosis, reinforcing concerns regarding prolonged and intensive ICS exposure(Price et al., 2019). In contrast, a study by Liu et al. (2016) found a potential protective effect of ICS among female COPD patients, suggesting that demographic and biological factors may modulate the skeletal impact of ICS therapy(Liu et al., 2016). Additionally, Chalitsios et al. (2021) reported that regular ICS use in asthma patients was significantly associated with a higher incidence of osteoporosis and fragility fractures compared to the general population(Chalitsios, Shaw, & McKeever, 2021).

This inconsistency presents a gap in the literature regarding which patient populations are most vulnerable, which ICS regimens confer the greatest risk, and what clinical measures may mitigate such risks. Furthermore, few reviews have synthesized these findings in a way that informs clinical decisions regarding the long-term safety of ICS use in the context of osteoporosis prevention.

Therefore, this review aims to critically evaluate the current evidence regarding the association between ICS use and osteoporosis risk by examining modifying factors such as ICS dosage, duration, molecular type, age, sex, and comorbidities. The review also seeks to develop a synthesized body of current evidence and propose risk-based considerations to support the development of evidence-informed guidelines for personalized and safe ICS prescribing, particularly for long-term use.

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2. RESEARCH METHODS

Study design

This literature review aimed to evaluate the relationship between inhaled corticosteroid (ICS) use and the risk of osteoporosis or bone fractures. The studies analyzed primarily consisted of observational designs, including case-control and cohort studies. Selection of core studies was based on their relevance to the research objectives, the clarity and completeness of reported data, and the presence of quantitative outcome measures such as odds ratio (OR), relative risk (RR), or hazard ratio (HR). A total of 6–8 key studies with comprehensive data were analyzed in depth in this review.

Search strategy

A search was conducted across electronic databases including PubMed, Scopus, and Web of Science. Keywords used included: "inhaled corticosteroids," "osteoporosis," "risk," and "bone fracture," combined using Boolean operators such as AND/OR to broaden the search results. The initial search yielded 50 articles. After removing duplicates and screening based on titles and abstracts, 36 articles were selected for further review. A subsequent assessment of full-text availability and content relevance narrowed the selection down to 28 articles that met the inclusion and exclusion criteria. The selection process is illustrated in a PRISMA flow diagram, outlining the stages of identification, screening, eligibility, and inclusion. Of the 28 articles, only 6 to 8 core studies were included in the systematic analysis based on quality, completeness of data, and relevance to the research objectives. Table 1 shows the inclusion and exclusion criteria. The literature search was conducted up to March 2025.

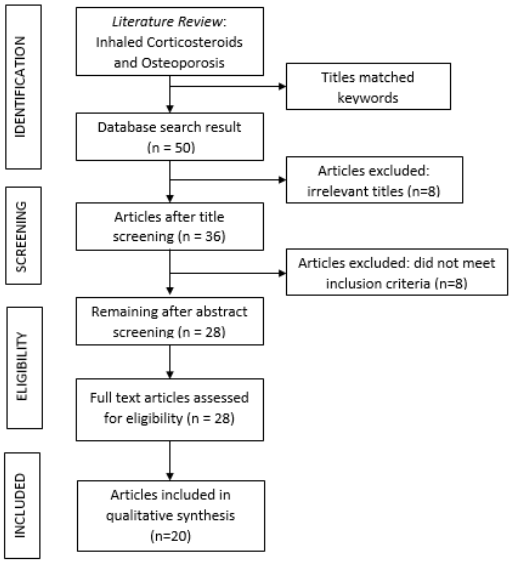

Figure 1. PRISMA Flow Diagram

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Eligibility criteria

Table 1. Inclusion and Exclusion Criteria

Category	Inclusion Criteria	Exclusion Criteria
Study design	Case control and cohort studies	Cross sectional studies, descriptive studies, case report/editorials
Population	Patient with osteoporosis or fractures related to BMD	Patient with other bone metabolism disorders not related to ICS
Intervention	ICS use with clearly reported dosage and duration	Use of systemic corticosteroid without concurrent ICS
Outcomes	Incidence of osteoporosis or decreased Bone Mineral Density (BMD) andfracture risk	Outcomes not focused on osteoporosis/fracture or lacking statistical measurements
Result	Outcomes reported with risk measures such as Odds Ratio (OR), Relative Risk (RR), or Hazard Ratio (HR)	Studies not reporting quantitative data or only presenting narrative reports without statistical analysis

Data Extraction

Data from articles that met the criteria were systematically identified and extracted, including author names, year of publication, study type, sample size, ICS dosage, duration of use, and key statistical outcomes such as OR, RR, and HR.

Data Analysis

The extracted data were analyzed descriptively and quantitatively. Results from each study were compared to assess the consistency of findings regarding ICS use and its association with decreased bone density or increased risk of osteoporosis.

3. RESULT AND DISCUSSION

A total of 50 articles were identified through the initial search, 28 articles met the inclusion criteria and were thoroughly analyzed. Based on methodological quality and data completeness, 6 to 8 articles were selected as core studies. These studies originated from various countries (United Kingdom, Sweden, Canada, Taiwan, and China) and employed cohort, case-control, and one meta-analysis design. The primary populations included patients with COPD, asthma, and mostly involved elderly patients.

The result showed that ICS use is associated with an increased risk of osteoporosis and bone fractures, particularly among older adults, those receiving high doses, and those with treatment durations of 12 months or longer. The most pronounced risks were observed with fluticasone and budesonide at doses of ≥500 µg/day.

Table 2 summarizes the key findings from each study, including the type of ICS, study design, and the reported risk measures (RR, OR, HR). Overall, high-dose ICS use demonstrated a significant association with reduced bone mineral density (BMD) or increased fracture risk. However, some studies also reported protective effects in specific populations, such as women with COPD(Liu et al., 2016).

Table 2. Summary of key studies on ICS and osteoporosis

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No	Title	Author	Study Type	Population	Type/Dose of ICS	Objective	Findings
1	Inhaled corticosteroids in copd and onset of type 2 diabetes and osteoporosis: matched cohort study	Price et al (2019)(Price et al., 2019)	Cohort	19.898 COPD patient in the UK (≥40 years)	Fluticasone propionate-equivalent; ≥500 µg/day	To evaluate the relationship between ICS and onset of osteoporosis and diabetes	High-dose ICS (≥500 µg/day) increased osteoporosis risk (dose-response significant); overall HR 1.13 (CI 0.93–1.39) was not statistically significant
2	Evaluating the association of osteoporosis with inhaled corticosteroid use in chronic obstructive pulmonary disease in Taiwan	Chiu et al (2021)(Chiu, Lee, & Chen, 2021)	Nested case-control study	58.048 cases and 174.144 controls from Taiwan NHIRD	High- and low-dose ICS (specific types not mentioned); analysis based on dose and duration	To assess ICS dose/duration association with osteoporosis in COPD	Overall ICS use increased risk (OR 1.053, p=0.0013); high-dose OR 1.085 (p<0.0001); low-dose reduced risk (OR 0.714)
3	Osteoporosis and fracture risk associated with inhaled corticosteroid use among Swedish COPD patients: the ARCTIC study	Janson et al (2021)(Janson et al., 2021)	Retrospective cohort	9.651 COPD patients in Sweden and 59,454 controls	Budesonide and fluticasone propionate; low dose <640 µg/day, high dose ≥640 µg/day	To assess osteoporosis/ fracture risk based on ICS dose	High-dose ICS increased osteoporosis and fracture risk (RR 1.52; CI 1.24–1.62); low dose also significant (RR 1.27; CI 1.13–1.56) vs. non-ICS
4	Long-term use of inhaled corticosteroids in COPD and the risk of fracture	Gonzalez et al. (2017)(Gonzalez et al., 2018)	Nested case-control	240.110 COPD patients in Quebec	Fluticasone-equivalent ≥1000 µg/day for ≥4 years	To assess long-term ICS use and fracture risk	Long-term high-dose ICS use (≥4 years) increased fracture risk (RR 1.10; CI 1.02–1.19)
5	Inhaled corticosteroids can reduce osteoporosis in female patients with COPD	Liu et al. (2016)(Liu et al., 2016)	Retrospective cohort	10.723 female COPD patients in Taiwan	Fluticasone & Budesonide; ≥60 mg total dose	To assess ICS effect on osteoporosis incidence in women	ICS reduced osteoporosis risk (HR 0.73; CI 0.63–0.84); protective effect increased with dose (P for trend = 0.0023)
6	Risk of Fracture and Osteoporosis in Patients With COPD and Inhaled Corticosteroids Treatment	Zhang et al. (2023)(Zhang et al., 2023)	Meta-analysis (26 RCTs)	61.380 COPD patients	Various ICS (in RCTs)	To examine ICS impact on fracture and osteoporosis risk	No significant increase in fracture (RR 1.10; CI 0.98–1.23) or osteoporosis (RR 0.93; CI 0.49–1.79)

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7	Effect of Fracture Risk in Inhaled Corticosteroids in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis	Peng et al. (2023)(Peng et al., 2023)	Systematic review and meta-analysis (44 RCTs)	87.594 COPD patients from 44 RCTs	ICS, ICS/LABA, and triple therapy (e.g., budesonide ≥320 µg BID, fluticasone furoate 100 µg QD)	To assess ICS-related fracture risk in COPD	ICS increased fracture risk (RR 1.19; CI 1.04–1.37); ICS/LABA: RR 1.30 (1.10–1.53); Triple therapy: RR 1.49 (1.03–2.17); Risk higher with ≥12 months duration, age ≥65, GOLD III, and high-dose budesonide/fluticasone furoate

In addition to the core studies, several supporting studies were analyzed to enrich the discussion context—particularly those involving pediatric populations, asthma patients, and studies with inconsistent findings.

Table 3. Supporting studies related to ICS and osteoporosis

No	Title	Author	Study Type	Population	Type/Dose of ICS	Objective	Findings
1	Bone mineral density and fracture risk with long-term use of inhaled corticosteroids in patients with asthma: systematic review and meta-analysis	Loke et al. (2015) (Loke, Gilbert, Thavarajah, Blanco, & Wilson, 2015)	Systematic Review & Meta-analysis	18 studies (7 RCTs, 11 observational); children and adults with asthma	Fluticasone, Budesonide, Mometasone, Beclomethasone (≥12 months use)	To assess the long-term effect of ICS on fracture risk and BMD	No significant association found between long-term ICS use and risk of fracture or BMD reduction in children and adults
2	Relationship Between Inhaled Steroid Use and Osteoporosis in Pediatric Asthma Patients	Tjahjono et al. (2024)(Tjahjono, Haydar, Yuliarto, & Oliviant o, 2024)	Cross-sectional	13 pediatric asthma patients (aged 5–18 years)	Fluticasone & Budesonide (≥3 months)	To analyze the correlation between ICS dose/duration and bone density	Strong negative correlation between cumulative ICS dose and BMD z-score (r = –0.827, p = 0.000)
3	Incidence of osteoporosis and fragility fractures in asthma: a UK population-	Chalitsios et al. (2021)(Chalitsios et al., 2021)	Population-based cohort	Asthma patients (UK CPRD database)	ICS (varied doses) & OCS	To assess the incidence of osteoporosis and fragility fractures in	Regular ICS use significantly increased the risk of osteoporosis (aHR 1.18) and fractures (aHR 1.12)

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	based matched cohort study					asthma patients	compared to the general population
4	Inhaled corticosteroids and risk of osteoporosis in late-middle-aged subjects: a multicenter European cohort study	Grosso et al. (2023) (Grosso et al., 2023)	Multicenter European cohort	3.004 subjects aged >55 years (ECRHS III)	ICS ≥12 months; median exposure ≥36,5 months	To evaluate the relationship between long-term ICS use and osteoporosis based on self-report	No increased risk of osteoporosis (OR = 1.02; 95% CI: 0.51–2.03); not significant even with ICS duration ≥36.5 months
5	Effect of inhaled corticosteroids on bone mineral density in patients with asthma	Watanabe et al. (2023)	Observational	40 adult asthma patients	Budesonide, Fluticasone, Ciclesonide (converted to fluticasone equivalent)	To evaluate the effect of ICS on BMD	No significant correlation between cumulative ICS dose and BMD; long-term ICS use considered safe

The findings of this review indicate a significant association between the use of inhaled corticosteroids (ICS) and decreased bone mineral density (BMD), as well as an increased risk of osteoporosis and fractures particularly in cases involving high doses and long-term use. These results are consistent with the theory of glucocorticoid-induced osteoporosis (GIOP), which suggests that corticosteroids disrupt bone metabolism by inhibiting osteoblast activity, increasing osteoclast activity, and impairing calcium and vitamin D homeostasis(Kobza et al., 2021).

Studies by Price et al. (2019) and Chiu et al. (2021) demonstrated that high-dose ICS use is statistically associated with increased osteoporosis risk, as shown by significant hazard ratios (HR) and odds ratios (OR)(Price et al., 2019),(Chiu et al., 2021). In contrast, Liu et al. (2016) reported a protective effect of ICS against osteoporosis in female COPD patients, highlighting the importance of gender and population characteristics in modulating risk potentially due to differences in hormonal levels (e.g., estrogen), drug metabolism, and nutritional status(Liu et al., 2016). Zhang et al. (2023) meta-analysis found no significant association between ICS use and risk of osteoporosis or fractures overall. This may be attributed to the heterogeneity in study designs and populations(Zhang et al., 2023). Conversely, Peng et al. (2023) reported a significantly increased fracture risk, particularly in patients receiving ICS/LABA combinations or triple therapy. The highest risk was observed in patients aged ≥65 years, with COPD GOLD stage III, and ICS use ≥12 months(Peng et al., 2023).

Among younger populations, such as children (Tjahjono et al., 2024) and young adults with asthma (Watanabe et al., 2023), findings were inconsistent(Tjahjono et al., 2024),(Watanabe et al., 2023). This suggests that the skeletal effects of ICS are more pronounced in older adults with severe comorbidities, especially those with COPD, than in otherwise healthy asthma patients. These findings emphasize the importance of individualized therapy and routine BMD monitoring for long-term ICS users. The type of ICS used also plays a critical role in determining risk. Janson et al (2021) found that both budesonide and fluticasone, even at low doses (≥640 µg/day), significantly increased the risk of osteoporosis

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and fractures compared to non-ICS users (RR 1.27; 95% CI 1.13–1.56), suggesting a dose-response effect(Janson et al., 2021).

Some studies found no direct link between ICS use and reduced BMD. Grosso et al. (2023), in a multinational cohort study, reported no significant increase in osteoporosis risk in older adults using ICS for over 36 months (OR 1.02; 95% CI 0.51–2.03)(Grosso et al., 2023). Similarly, Watanabe et al. (2023) found no correlation between cumulative ICS dose and BMD in adult asthma patients(Watanabe et al., 2023). These findings suggest the existence of a threshold dose or duration beyond which ICS may exert systemic effects, and point to possible protective factors such as concurrent supplementation, lifestyle interventions, or additional therapies.

Bone density monitoring via dual-energy X-ray absorptiometry (DXA) should be an integral part of long-term management in ICS users, particularly those at high risk. Rational ICS use involves prescribing the lowest effective dose, minimizing treatment duration, and regularly assessing osteoporosis risk factors. Complementary strategies, including healthy lifestyle education, weight-bearing exercise, and calcium and vitamin D supplementation, are highly recommended for prevention. These findings emphasize the importance of individualized therapy and routine BMD monitoring for long-term ICS users. Further evidence from Ozcakir et al. (2020)(Ozcakir, Sigirli, Ursavas, & Uzaslan, 2020) and Chalitsios et al. (2021)(Chalitsios et al., 2021) highlight the role of ICS in reduced BMD and increased fracture risk in COPD and asthma patients, respectively.

Variations in findings across populations and studies underscore the need for further research, especially through long-term prospective cohort designs that can control for confounding variables such as systemic corticosteroid use, nutrition, lifestyle or additional therapies, as explored in Grosso et al. (2018)(Grosso et al., 2018) and confirmed in meta-analyses by Zhang et al. (2023)(Zhang et al., 2023) and Peng et al. (2023)(Peng et al., 2023). Such studies could help establish safe thresholds for ICS dose and duration with respect to bone health and provide evidence-based recommendations for safer clinical practices.

ICS remains a cornerstone therapy for chronic respiratory diseases such as asthma and COPD, administered via inhalation to reduce systemic side effects compared to oral or injectable corticosteroids. ICS effectively reduces exacerbations and symptoms, particularly in patients with elevated blood eosinophil levels, and is commonly used in combination with LABA and/or LAMA for bronchodilation and anti-inflammatory effects(Aljubran, Whelan, Glaum, & Lockey, 2014). However, ICS use especially at high doses and over long durations can contribute to metabolic complications, including osteoporosis(Gregson et al., 2022). ICS affects bone by reducing osteoblast activity, increasing osteoclast activity, inhibiting calcium absorption, increasing urinary calcium excretion, and suppressing sex hormone production. High-dose ICS also downregulates type I collagen synthesis, which is vital for bone strength.

Clinical recommendations include: (1) using the lowest effective ICS dose; (2) calcium and vitamin D supplementation; (3) routine BMD monitoring; (4) considering anti-resorptive agents in high-risk patients; and (5) conducting thorough risk assessments before initiating high-dose ICS especially in individuals with osteoporosis risk factors. With an appropriate approach, the risk of ICS-induced osteoporosis can be minimized without compromising the treatment effectiveness of chronic respiratory conditions.

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4. CONCLUSION

This review concludes that the use of inhaled corticosteroids (ICS), particularly at high doses and over long durations, may be associated with reduced bone mineral density (BMD) and an increased risk of osteoporosis and fractures. The findings highlight the role of glucocorticoid-induced bone metabolism disruption and emphasize that older adults with chronic respiratory diseases, especially COPD, are at the greatest risk. While some studies reported no significant association, the inconsistencies likely reflect differences in study populations, ICS types, dosing, and other confounding factors. These findings underscore the importance of individualized risk assessment, regular BMD monitoring, and the implementation of preventive strategies such as calcium and vitamin D supplementation. This review contributes to clinical practice by reinforcing the need for cautious and rational ICS use to balance therapeutic benefits with long-term bone health risks.

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