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REVIEW

Inhaled corticosteroids effects on bone in asthmatic and COPD patients: a quantitative systematic review

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Abstract Deleterious effect of oral corticosteroids on bone has been well documented, whereas this remains debated for inhaled ones (ICS). Our objectives were to analyze the effects of ICS on bone mineral density, fracture risk and bone markers. We performed an exhaustive systematic research of all controlled trials potentially containing pertinent data, peer-reviewed by a dedicated WHO expert group, and comprehensive meta-analyses of the data. Inclusion criteria were ICS, and BMD/markers/fractures in asthma/chronic obstructive pulmonary diseases (COPD) and healthy patients. Analyses were performed in a conservative fashion using professional dedicated softwares and stratified by outcome, study design and ICS type. Results were expressed as standardized mean difference/effect size (ES), relative risk (RR) or odds ratio (OR), depending on study design and outcome units. Publication bias was investigated. Twenty-three trials were reviewed; 11 papers fit the inclusion criteria and were assessed for the main analysis. Quality scores for the randomized controlled trials (RCTs) were 80%, 71% for the prospective cohort studies, and 78% for the retrospective cohort and cross-sectional studies. We globally assessed ICS effects on BMD and found deleterious effects: ES = 0.61 ($p = 0.001$) for healthy subjects, and ES = 0.27 ($p < 0.001$) for asthma/COPD patients. For these patients, this effect was 0.21 ($p < 0.01$) at the lumbar spine, and 0.26 ($p < 0.001$) at the hip or femoral neck. A single study evaluated the impact of ICS on hip fracture and reported an increased OR of 1.6 (1.24; 2.03). Lumbar fracture rate differences did not reach the level of statistical significance: 1.87 (0.5; 6.94). Osteocalcin and PICP were decreased and ICTP, pyridinoline and deoxypyridinoline levels were not significantly affected. Budesonide (BUD) appeared to be the ICS inducing the less deleterious effects on bone, followed by beclomethasone dipropionate (BDP) and triamcinolone (TRI). Publication bias investigation provided non-significant results. In our meta-analyses, BUD at a mean daily dose (SD) of 686 μg (158 μg), BDP at 703 μg (123 μg) and TRI at 1000 μg (282 μg) were found to affect bone mineral density and markers in patients suffering from the two major respiratory diseases. These findings could have practical implication in the long-term management of asthmatic and COPD patients.

Keywords Bone · Inhaled corticosteroids · Meta-analysis · Osteoporosis

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Introduction

Glucocorticoid (GS)-induced osteoporosis has been recognized since 1932 when Cushing first described skeletal demineralization as a characteristic feature of adrenal hyperplasia secondary to pituitary tumors producing adrenocorticotrophic hormone [1]. Because of the low prevalence of the Cushing syndrome, glucocorticoid-induced bone loss did not become a significant problem until these agents began to be widely used and when patients on glucocorticoid treatment appeared to be more likely to develop fractures [2]. Consequently, for over five decades, osteoporotic fractures were recognized as one of the most devastating complications of chronic treatment with parenteral or oral corticosteroids [3].

Inhaled corticosteroids (ICS) have become the mainstay in the long-term treatment of asthma and chronic obstructive pulmonary diseases (COPD) [4]. They are highly effective and are often required for long-term disease control. One in three patients treated for asthma in the UK is taking an ICS on a regular basis, and a third of them receive high doses of ICS (800 μg budesonide or beclomethasone dipropionate or 500 μg or more fluticasone per day) [5]. There is an increasing scientific concern about systemic effects of long-term ICS treatment, including bone loss. Relatively few evidence-based publications are available on the effects of ICS on bone metabolism as compared with long-term oral or parenteral glucocorticoid therapy, an unequivocal leading cause of iatrogenic osteoporosis.

Recent consensus reports recommend an increasing use of ICS in the management of asthma [6, 7]. Furthermore, COPD or asthma patients require long-term exposure to ICS, and no long-term study is currently available to appraise their safety profile. Furthermore, conflicting results from shorter trials made it difficult both for the scientist and the medical doctor to evaluate whether the benefits of ICS are overcome by their skeletal side effects.

Our objective was to quantify the evidence of the relationship between the intake of inhaled corticosteroids and their effects on bone formation and resorption marker levels, bone mineral density and fracture risk.

Methods

An exhaustive search of all potentially appropriate publications was performed, following a predefined protocol. Electronic sources included Medline and Premedline, Biosis Preview, Healthstar, Embase, Cochrane Library of Randomized Controlled Trials, Current Contents, EBM reviews and Internet. Generic keywords, according to the thesaurus of each individual database, were generated. Since all reports are not indexed in these databases, we conducted a manual search of the references section of each of the reports. The strategy was derived from the sensitive search strategy currently recommended by the Cochrane Collaboration Musculoskeletal Group and the results were added to those provided by another validated method [8].

We retrieved any controlled study dealing with bone mineral density, fractures or bone turnover markers in asthma, COPD or healthy adults allocated to inhaled corticosteroids or inactive control. Although RCTs are the mainstay of evidence-based medicine, we wished to have an overview of the available scientific material, our assertions being based on RCT data. Osteocalcin, bone-specific alkaline phosphatase (BALP) and procollagen I carboxy- and N-terminal extension peptides (PICP, ICTP), urinary pyridinoline (Pyr) and deoxypyridinoline (D-Pyr) were taken into account as bone metabolism markers. We first focused on investigations in which included subjects were asthmatics or COPD patients who did not use either ICS or oral corticosteroids for at least 6 months, allocated to ICS or inactive control during the whole study duration for prospective trials including RCTs. The rationale for this was to avoid the potentially confounding effects of differential bone status and factors affecting bone turnover, due to the illness itself and/or previous or concomitant medications. Studies with healthy controls were analyzed as a secondary endpoint to clarify this point. Moreover, bone mineral density had to be assessed by dual X-ray photon absorptiometry (DXA). The studies had to be performed between January 1985 and February 2002. We had no limitations on language or journal.

The publications retrieved were presented as complete reports (abstracts were discarded) and discussed for methodological standards and inclusion criteria compatibility in a specifically dedicated WHO meeting including eight leading experts in the fields of Rheumatology, Pneumology, Endocrinology, Public Health and Quantitative Epidemiology. Divergences were solved by consensus. Quality scoring was performed using the Jadad score [9] for RCTs. As a preliminary endpoint of the WHO meeting, retrospective cohort and cross-sectional studies have been decided, by consensus, to be scored on items presented in Tables 1 and 2.

Data extraction was performed by two independent authors (F.R., O.B.) to ensure for accuracy in data encoding. Values from intention-to-treat analyses were systematically used when available; otherwise, we took into account per-protocol results. This approach, as well as the combination models used, favored conservative statistical conclusions: Hunter-Schmidt method for effect-size calculation using Hedges's d-corrected results instead of Cohen's d when required. Results expressed, for instance, as $p < 0.05$ were encoded $p = 0.049$. In this particular meta-analysis this

Table 1 Quality scoring process for retrospective cohort and cross-sectional studies. *ICS* inhaled corticosteroid

Item	Mentioned	Clearly described	Judged appropriately taken into account	Score
Confounding factors	+1	+0.5 if listed	+0.5 if used as inclusion criteria or in multivariate analysis	
Duration of retrospective follow-up	+1	+1		
Evaluation of ICS consumption	+1	+1		
Methods for outcomes assessment	+1	+0.5 if method described	+0.5 if method judged currently adequate	
				/8%

Table 2 Quality scoring process for non-randomized prospective cohort studies

Item	Mentioned	Clearly described	Judged appropriately taken into account	Score
Homogeneity between groups after randomization	+1	+0.5 if listed	+0.5 if homogeneity assessed by paired test	
Confounding factors	+1	+0.5 if listed	+0.5 if used as inclusion criteria or in multivariate analysis	
ICS consumption	+1	+1 if ICS consumption controlled		
Duration of follow-up	+1	+1		
Methods for outcomes assessment	+1	+0.5 if method described	+0.5 if method judged currently adequate	
Dropouts and withdrawals	+1	+1		
Intention-to-treat analysis	+1	+1		
				/14%

approach led to conservative statistical conclusions based on the null hypothesis that inhaled corticosteroids have no effects on all considered endpoints.

Results were analyzed by design and outcome class: continuous outcomes by effect size (standard difference, ES); dichotomized results by relative risk (RR); or odds ratio (OR) for retrospective studies. When mean differences from "before–after" measures and their related standard deviations were not available in the report, we used the "after" values, under the strict condition of an equivalence of the means assessed at study beginning, at $p > 0.75$; otherwise, the studies were rejected. Univaried weighted regression analyses of ES against the following predictors were done: asthma/COPD patients; percentage of smokers; allowed ICS; dose; mean age at inclusion; and follow-up time. A non-parametric model was used (Spearman's r). Weights were taken from meta-analysis statistics. The alpha risks were set at 5% for association and 10% for heterogeneity tests. The global and individual estimators were surrounded by their 95% confidence intervals. Bone loss rates were appraised by regressing the difference in bone loss between exposed and control groups against the respective study duration. Publication bias was statistically explored by funnel plot drawing (log of the relative risks against their precision, symmetrical if no publication bias is present) and by regressing standard normal deviates of the effects against their precision (not different from zero on the y axis if no publication bias is present) [10]. Statistical operations were performed using Comprehensive meta-analysis version 1.0.25 (Biostat, Englewood, NJ), and Statistica 6.0 (Statsoft, France), by a skilled analyst.

Results

The bibliographic search steps led to the identification of 23 publications that were peer-reviewed by the WHO expert group. Once inclusion criteria were applied, 11 papers [11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21] were kept and assessed for methodological standards, whereas 12 were withdrawn [22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33] (Tables 3, 4). The mean quality score for the five RCTs was 80%, the two prospective cohort studies 71.4% and the four retrospective cohort and cross-sectional studies 78.05%. The investigated corticosteroids were budesonide (BUD), beclomethasone dipropionate (BDP), triamcinolone acetonide (TCA) and fluticasone (FLU).

As an overview, we computed the results of the combination of all trials on the effects of ICS on bone mineral density (BMD), regardless of the measurement site and study design. We found a significant deleterious effect (ES = 0.271, $p < 0.0001$; Fig. 1). Individual effects were found to be statistically homogeneous ($p_{het} = 0.62$). Two studies [16, 19] included specifically smokers, who were older than in other studies. When removing these two studies from the combination model, the global estimator decreased and became non-significant. This suggests that the cumulative effect of aging and smoking, and of a higher cumulative dose, might explain a part of the differential effect of ICS on bone.

The results were stratified by study design and measurement site. At the lumbar spine, the combination of all relevant data provided similar results for both prospective or retrospective and prospective studies. Using the whole data subset, the effect was 0.216; $p = 0.02$ (Fig. 2). The combinations of RCTs separately or all prospective studies provided ES = 0.21 at $p = 0.007$ and $p = 0.004$, respectively. In these studies, 20% of asthmatic patients and 80% of COPD patients were reported to be smokers. Asthmatic patients were logically younger than COPD ones. The eight considered ES were normally distributed (Kolmogorov-Smirnov $d = 0.07$, NS) and homogeneous (Cochran's Q, $p = 0.90$). The only cross-sectional study [21] did report non-significant and conflicting results, i.e. BMD was non-significantly reduced in women and increased in men.

At the femoral neck or the hip, BMD was significantly decreased (ES = 0.275, $p < 0.01$) in the summary analysis (Fig. 3). In RCTs, ES was 0.266 at $p < 0.001$. When adding the two non-randomized trials in this subset this estimator became ES = 0.263 at $p < 0.01$. The combination of the results of the two relevant cross-sectional studies furnished an almost significant estimator: ES = 0.44 at $p = 0.063$.

Four controlled studies provided information on the relationship between ICS treatment and fractures rates. Combining RCTs, the relative risk of experiencing a spinal fracture was 1.86 [0.51; 6.8] (Fig. 4). When restricting to spinal fractures reported in retrospective and cross-sectional trials we found an OR = 1.21 [0.96;

Table 3 Summary of controlled trials on inhaled corticosteroids and bone metabolism matching inclusion criteria for primary analysis. *RCT* randomized controlled trials, *DB* double-blind method mentioned, *MC* multicentric trial, *COPD* chronic obstructive pulmonary disease, *FEV_1* forced expiratory volume in 1 min, *FVC* forced vital capacity, *CROSS* cross-sectional study, *PROSP* prospective cohort study, *OCS* oral corticosteroid, *ICS* inhaled corticosteroid, *FLU* fluticasone, *BDP* beclomethasone dipropionate, *BUD* budesonide, *TCA* triamcinolone acetonide, *BMD* bone mineral density, *PBO* placebo group, *NS* non-significant effect, *S* significant effect, *ICTP* type-I collagen carboxy-terminal telopeptide, *LS* lumbar spine, *PICP* procollagen type-I carboxy terminal propeptide, *Troch* trochanteric region

Reference	Design	Inclusion criteria	ICS/dose = sample size used for calculations	Duration (years)	Variables analysed/ results (between ICS and control groups and in selected analyses)	Inclusion status
[19]	RCT, MC, DB	Smokers aged 40–69 years with COPD with a ratio of FEV_1 of less than 0.7 FVC, and a value of FEV_1 that was 30–90% of the predicted value	TCA at 1200 μg/day = 158, placebo = 170	3	BMD LS: S; BMD FN: S	Included
[16]	RCT, DB, MC	Adults with COPD aged 30–65 years, smoking > 5 cigarettes for > 10 years, 0.5 < FEV < 1 after bronchodilator	BUD at 800 μg/day = 634, PBO = 643	3	FEV decrease slope: NS; BMD LS: NS; fractures: NS	Included
[14]	RCT	Men (18–50 years) and women (18–40 years) with diagnosed asthma for at least 6 months before enrollment, an FEV_1 of at least 60% of the predicted value and limited previous CS therapy	FLU at 1000 μg/day = 32, PBO = 32	2	BMD LS: NS; osteocalcin: NS	Included
[13]	RCT	Adults with COPD aged 18–60 years, without other major illness; FEV_1 between 4.5 and 1.64 SD below the predicted value; concentration in histamine causing a 20% decrease in FEV_1 ≤ 8 mg/ml	BDP at 800 μg/day = 70, placebo = 41	2.5	PICP: NS; ICTP: S	Included
[18]	Open RCT, MC	Adults with mild asthma aged 20–60 years, no steroid treatment for 3 months	BUD at 400 μg/day = 87, BDP at 500 μg/day = 74, asthmatic controls = 78	2	BMD LS: NS; BMD FN: NS; fractures: NS; serum osteocalcin: S for BDP vs controls; F-DPD: NS; F-PYD: NS	Included
[17]	PROSP	Adult with COPD aged 30–80 years who never had OCS treatment	BDP at 800 μg/day = 11, BUD at 800 μg/day = 12, COPD controls = 10	1	BMD LS: NS; BMD Hip: NS; serum osteocalcin: S; PAL: S	Included
[12]	PROSP	Women with a diagnosis of asthma aged 18–45 years old, and who had had ten or more menstrual periods during the preceding year; and with no disease or medication affecting bone metabolism	TCA at 800 μg/day = 42, asthma controls = 28	3	BMD LS: NS; BMD FN: NS; BMD total hip: S; BMD Troch: S	Included

[20]	RETRO	ICS users aged > 18 years, not having required OCS in the 6 months before the retrospective cohort settlement	BDP, BUD at 700 μg/day = 28,815, bronchodilatator users = 108,786	Mean retrospective follow-up = 1.7 years	Colle's fracture: NS; hip fracture: S; vertebral fracture: NS; other fracture: S	Included
[21]	CROSSRETRO	Asthmatic adults aged 20–40 years with a documented history of asthma, requiring ICS for at least 5 years and having no systemic steroids for 6 months	BDP, BUD at 620 μg/day = 47, β_2 only control group = 34	Mean retrospective follow-up = 6–9 years	BMD LS (L3) women: 0.06; BMD FN: NS; BMD radius: NS; osteocalcin (women): S; urinary deoxypyridinolone: NS	Included
[15]	CROSS	Men older than 50 years with a primary diagnosis of COPD, a FEV_1/FVC ratio of < 70%, a smoking history of at least 20 pack-years and a minimum of six refills of a beta-agonist inhaler within the past year	ICS = 70, COPD controls = 117	Mean ICS use duration = 3.5 years (SD 2.6 years)	Vertebral fractures: NS	Included
[11]	CROSS	Asthmatic adults aged 25 years or more not requiring systemic treatments for 1 year before the study	BDP, BUD at800 μg/day = 18, asthmatic controls using bronchodilatator only = 18	–	BMD FN: NS; osteocalcin: S; urinary pyridinoline: NS; urinary deoxypyridinoline: NS	Included

1.67] (Fig. 5). Hip fractures were investigated in a single retrospective study which provided a small but highly significant OR at 1.6 [1.24; 2.03].

When regressing the differences in bone loss rates at lumbar spine, femoral neck and hip between exposed and control subjects against the trial's duration (in months), the three slope coefficients were −0.028 for triamcinolone (at mean dose = 1 mg/day), –0.016 for beclomethasone (at mean dose = 680 μg/day) and –0.010 for budesonide (at mean dose = 646 μg/day) percent per month. (Fluticasone was investigated in a single study fitting our inclusion criteria which did not provide adequate data for this analysis.) These unadjusted slopes reflected the monthly difference in the percentage of decrease in BMD between ICS and control groups in the prospective studies furnishing the highest degree of evidence among included trials. The three significant predictors of ES in the univaried regression analysis were dose (r = 0.873), budesonide consumption (r = 0.82) and TCA consumption (r = 0.748). The TCA consumption provided the highest overall bone loss, followed by beclomethasone and budesonide.

Serum osteocalcin was found to be globally reduced among ICS users: ES = 0.383 at $p = 0.01$ (Fig. 6). This point has been confirmed in the subgroup meta-analyses: while restricting to RCT: ES = 0.25, $p = 0.043$ as well as for prospective, retrospective cohort ones and cross-sectional ones. The effects on urinary Pyr (ES = 0.03, $p = 0.77$) and D-Pyr (ES = 0, $p = 0.93$) levels did not reach statistical significance when comparing BUD, BDP and placebo groups, nor did they show any deleterious trends in the two studies providing this information [18, 21]. The PICP level was increased in the prospective cohort study by Struijs and Mulder [17] (ES = 1.18 at $p = 0.01$) while not in the cross-sectional one by Wisniewski et al. [21] (ES = 0, $p = 1$). The ICTP levels were non-significantly increased and significantly decreased in the available prospective cohort study [17] and the available RCT [13]: ES = 0.44/$p = 0.16$ and ES = −0.51/$p = 0.01$, respectively. Whereas BALP was significantly decreased in the study by Struijs and Mulder [17] (ES = 0.47, $p = 0.04$), it was not in the cross-sectional study by Hanania et al. [11].

The obtained ES in studies, including asthmatic or COPD patients, were normally distributed (Kolmogorov-Smirnov d = 1.76, $p < 0.05$). When regressing standard normal deviates against precision, the intercept on the y axis was not different from zero, at $p > 0.10$ (Fig. 7). Notwithstanding the limited power of this statistical test, these findings were in line with the null hypothesis that the published evidence in this subgroup does not appear to be prone to bias.

Discussion

The efficacy and the safety of inhaled corticosteroids in asthma and COPD have been documented in more than 116 articles over the past 12 years. The conclusions have

Table 4 Summary of controlled trials on inhaled corticosteroids and bone metabolism not matching inclusion criteria for primary analysis. *WT* Ward's triangle, *DXA* dual-energy X-ray absorptiometry

Reference	Design	Inclusion criteria	ICS/dose = sample size used for calculations	Duration	Variable sanalysed/results (between ICS and control groups and in selected analyses)	Inclusion status
[22]	Open RCT, MC	Children with symptoms of asthma/wheezing aged 0.5–16 years that had commenced no longer than 12 months before the study, na to prior prophylactic therapy and having no concomitant illnesses	BDP or BUD at 400 μg/day = 26, β_2 only control group = 29	6 months	Urinary pyridinoline/creatinine: S; urinary deoxypyridinoline: S; BMD (ultrasonometry): S	Not included: children; no BMD assessment by DXA
[23]	RCT	Non-smoking healthy subjects who had normal pulmonary function, no metabolic disorders, not using drugs known to affect renal or skeletal metabolism, and who had never used either oral and inhaled corticosteroids	BUD at 1200 μg/day = 20, BUD at 2400 μg/day = 20, placebo = 8	1 month	Osteocalcin: n/a; urinary hydroxyproline: n/a	Included in secondary analysis: healthy patients
[24]	RCT, DB	Healthy subjects asked to exclude milk and dairy products from their diet during the study	BUD at 400 μg/day = 10, BUD at 1600 μg/day = 10, placebo = 10	2 weeks	Osteocalcin: S	Included in secondary analysis: healthy patients
[25]	RCT, MC, DB	Patients aged 50–75 years with diagnosed COPD, currently smoking or ex-smokers with a history of equivalent to at least 10 pack-years and chronic bronchitis	FLU at 500 μg/day = 142, placebo = 139	6 months	No bone-related outcome	Not included: no bone-metabolism-related outcome
[26]	RCT	Healthy premenopausal adult women aged 21–41 years with no history of use of any topical, inhaled or oral GC in the previous 3 months	BUD at 400–1600 μg/day = 7,BDP at 500–2000 μg/day = 7, placebo = 7	2 weeks	Osteocalcin: NS between groups; S for drug-dose interaction (BDP)	Included in secondary analysis: healthy volunteers
[27]	PROSP	Adults with bronchial asthma aged 40–60 years who had no systemic administration of ICS for at least 1 year	BDP 500 μg/day = 36, healthy controls = 45	2 years	BMD LS post-menopausal: S; BMD LS pre-menopausal: NS; osteocalcin: S; F-PYD: NS; F-DPD: NS; BMD LS: NS	Included in secondary analysis: healthy controls
[28]	PROSP	Non-smoking women aged 43–67 years with newly diagnosed asthma, who had no previous courses of CS. No history of fracture nor nutritional, metabolic, renal disease, drug affecting bone metabolism	BDP at 1000 μg/day = 19, healthy controls = 19	1 year	BMD FN: NS; BMD Troch: NS; BMD WT: NS	Included in secondary analysis: healthy controls

[29]	PROSP	Outpatients with chronic moderate to severe asthma aged 18–50 (men) and 18–40 years (women)	FLU at 1000 μg/day = 17, BDP at 2000 μg/day = 16, low dose ICS = 16, oral CS = 8, healthy controls = 7	2 years	BMD LS: NS; BMDFN: NS	Not included:inadequate control group
[30]	PROSP/ CROSS	Asthmatic patients taking ICS for more than 1 year	BDP or BUD at 700 μg/ day = 48, healthy controls = 48	2 years (longitudinal part)	BMD LS (L2–L4): NS	Included in secondary analysis: healthy controls; ICS consumption before inclusion
[31]	RETRO	Subjects with diagnosed asthma of varying severity for more than 2 years. The diagnostic had to meet the American Thoracic Society criteria	BDP, BUD at 800 μg/ day = 37, asthmatic controls = 37	Mean retrospective follow-up = 18 months	BMD LS: NS; BMDFN: NS; BMD WT: NS; osteocalcin: S	Not included:controls allowed for ICS intake
[32]	RETRO	Young premenopausal adults with diagnosed bronchial asthma requiring ICS for more than 3 months. No chronic systemic CS use	BDP, BUD at 1100 μg/day = 30, healthy controls = 30	Mean retrospective follow-up = 40 months	BMD LS: S; BMD FN: S; BMD Troch: S; BMD WT: S	Included in secondary analysis: healthy controls
[33]	CROSS	Prepubertal asthmatic children aged 4–12 years not suffering of any other illness	ICS at > 800 μg/day = 12, asthmatic controls with no ICS for 6 months = 10	Mean ICS duration = 5.4 years (SD 2.7 years)	BMD LS: NS	Not included: children

been almost identical: asthmatic patients who regularly use low doses of inhaled corticosteroids dramatically reduce their risk of serious respiratory complications. The compounds are well tolerated but lead to minor bone metabolism marker alteration in studies lasting, at best, several years. The ICS being successfully used for reducing the mortality among treated patients, it was not surprising that only a limited number (5) of complex randomized controlled trials specifically assessing their effects on bone density and metabolism matching our inclusion criteria were found. Furthermore, we were unable to find any prospective study assessing simultaneously markers, BMD and fracture incidence.

In a recent meta-analysis by the Cochrane Airways Group, Jones et al. [34] found no effect of a 2- to 3-year administration of ICS on biochemical markers of bone turnover, BMD and the development of fractures in several cohorts of asthma or COPD patients. The study was primarily aimed at the evaluation of the relationship between inhaled CS and bone turnover markers, in healthy, asthmatic or COPD subjects. Lipworth et al. [35] qualitatively reviewed the available literature in this field and concluded that inhaled corticosteroids, especially fluticasone propionate, exhibit dose-related adrenal suppression, a well-recognized risk factor for bone loss [36]. In the study by Kerstjens et al. [13], no detrimental long-term effect of inhaled corticosteroids was found using five parameters of bone metabolism (BALP, osteocalcin, PICP, ICTP and urinary hydroxyproline/creatinine ratio). The authors point out that long-term changes in bone turnover during treatment with ICS should not be extrapolated from short-term studies dealing with a single serum marker of bone metabolism, and emphasize the need for focusing on well-designed long-term studies including bone densitometry as primary outcome, before quoting detrimental effects of inhaled corticosteroids on bone metabolism. They found no evidence of increased risk of loss of BMD or fractures, nor any significant change in osteocalcin at conventional doses of inhaled corticosteroids. The limitations of studies in this area include: the difficulty in quantifying the confounding effect of previous systemic CS; the likelihood of a non-linear effect which would lead to short-term studies of newly treated patients overestimating the long-term effects on bone; and the evaluation of markers in healthy volunteers exaggerating the effect due to a higher proportion of ICS reaching the systemic circulation in individuals with normal lung function.

On the other hand, recent interventional studies of high methodological quality have provided new elements in this field. Israel et al. [12] found a significant correlation between triamcinolone acetonide treatment and bone loss at both the total hip and trochanter. The Lung Health Study Research Group [19] provided similar evidence and the inclusion of these two studies raised the power of our meta-analyses. This particular fact, and our different inclusion criteria, might explain the discrepancies between our findings and the ones of Jones et al. [34] and Lipworth

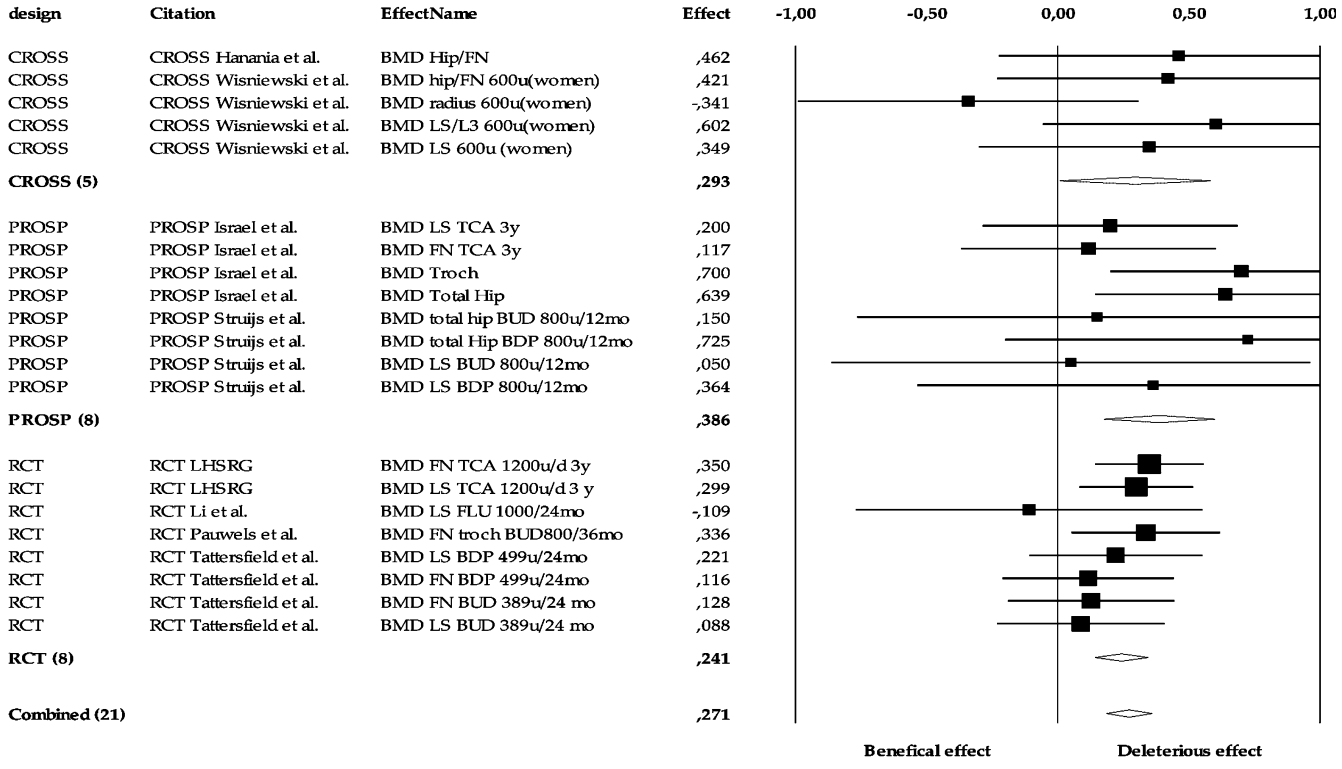

Fig. 1 Overview of the data available from studies on ICS impact on bone mineral density

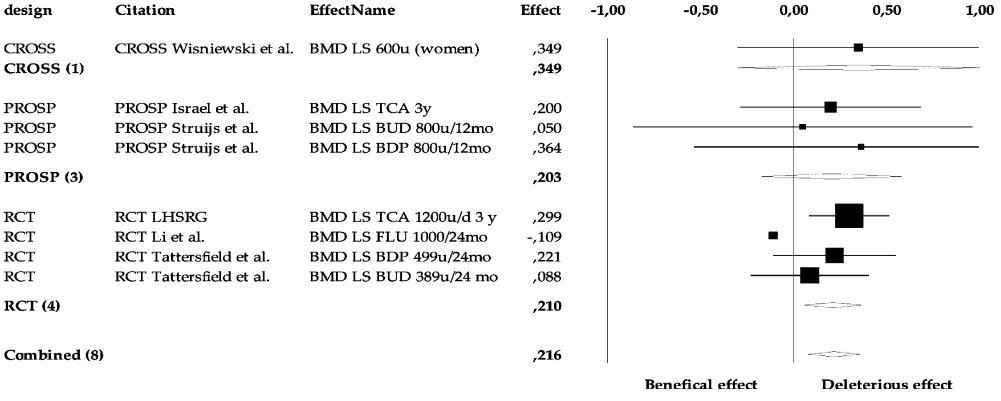

Fig. 2 Impact of ICS consumption on spinal bone mineral density

et al. [35]. Our goal was to provide an overview of the scientific material the physician or the researcher could use for decision making, by performing an exhaustive quantitative synthesis, stratified by study design, i.e. the associated level of evidence.

As a first result, we found that inhaled corticosteroids, at pharmacological doses, resulted in significant negative effect on lumbar spine mineral density in the quantitative synthesis of prospective controlled studies of a mean duration of 2.33 years. In the multivariate regression of trials characteristics against obtained ES, TCA and dose were significant predictors of a higher bone loss rate and BUD a smaller bone loss rate. This analysis was largely underpowered by using such summarized data, which might explain that the "time" parameter was not significant. Time ranges were also too restricted to extrapolate our results to the long term, but effect–time response was highlighted by linear regression on a basis of 40 months. In our meta-analysis, an increasing dose of ICS and a longer exposure were found to be directly linked to bone loss, which was already reported in several high-quality publications stating the time chart of bone loss to cumulative ICS dose [11, 18, 21]. In the cross-sectional study by Wisniewski et al. [21] lumbar spine BMD assessed at L3/L4 in women was reduced vs control, whereas BMD in men appeared to be non-significantly increased. This might be related with the fact that women and men had received a mean of

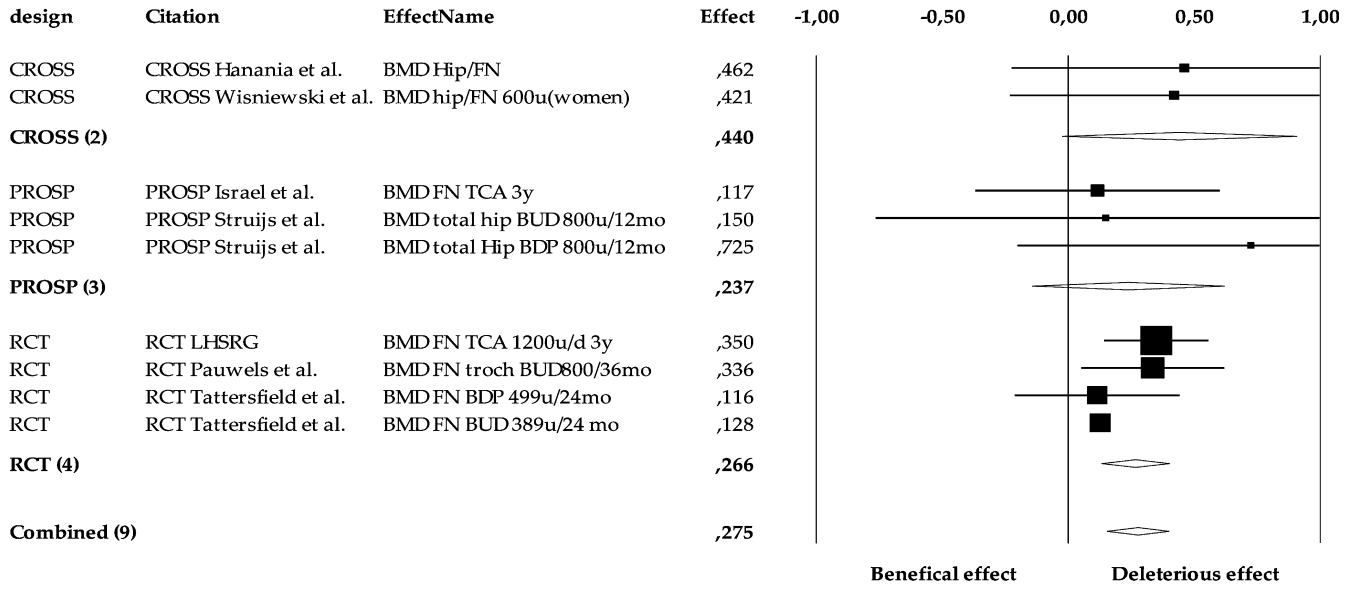

Fig. 3 Impact of ICS consumption on hip or femoral neck bone mineral density

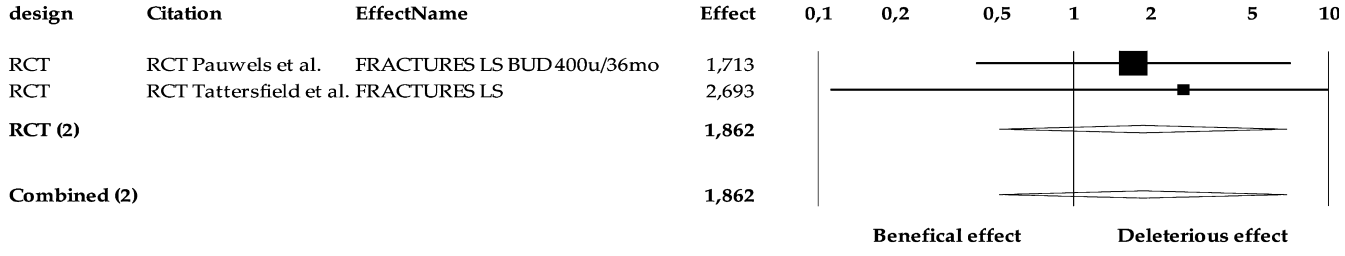

Fig. 4 Relative risk for spinal fracture while allocated to ICS versus placebo

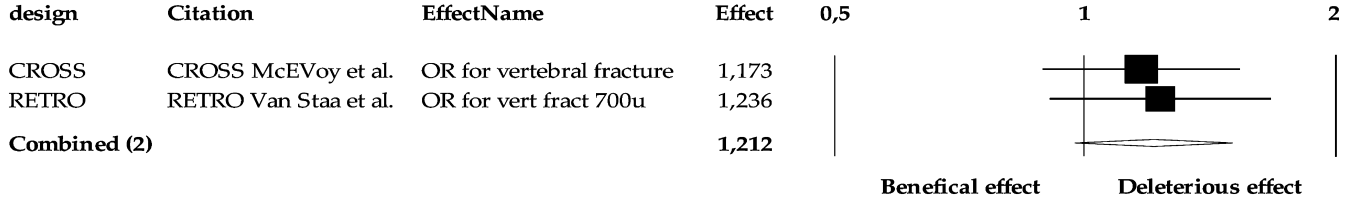

Fig. 5 Odds ratio for being exposed to ICS depending on fracture rates

2.46 and 1.33 previous courses of oral corticosteroids, respectively. Half of the women had received oral CS, whereas this was only the case in one-third of the men.

We focused then on hip and femoral neck mineral density, which provided conflicting results depending on study designs. The combination of the four prospective studies provided significant results while the two cross-sectional studies led to positive results. When suppressing the estimator for men in the study by Wisniewski et al. [21], the global estimator became nearly significant ($p = 0.063$), but twice higher than the value of the one extracted from prospective trials (0.44 vs 0.266). Considering the design and the extremely reduced sample sizes of these trials, we believe this might be attributable to a "small-study effect" (i.e. an overestimation of the ES by underestimation of the common variability of the observed differences often biasing small, short-term studies). With prospective studies delivering a higher degree of evidence than retrospective and cross-sectional studies, we concluded that ICS consumption at a mean duration of 2.5 years reduced hip and femoral neck mineral density.

We observed no significant association between ICS intake and fracture risk in the global combination of the four available studies [15, 16, 18, 20]. On the basis of a lifetime exposure to such compounds, it was not surprising to obtain such results, the mean duration of the trials being only 2.5 years. Moreover, osteoporotic fractures were specifically addressed, but osteoporosis being actually considered as a risk factor for fractures,

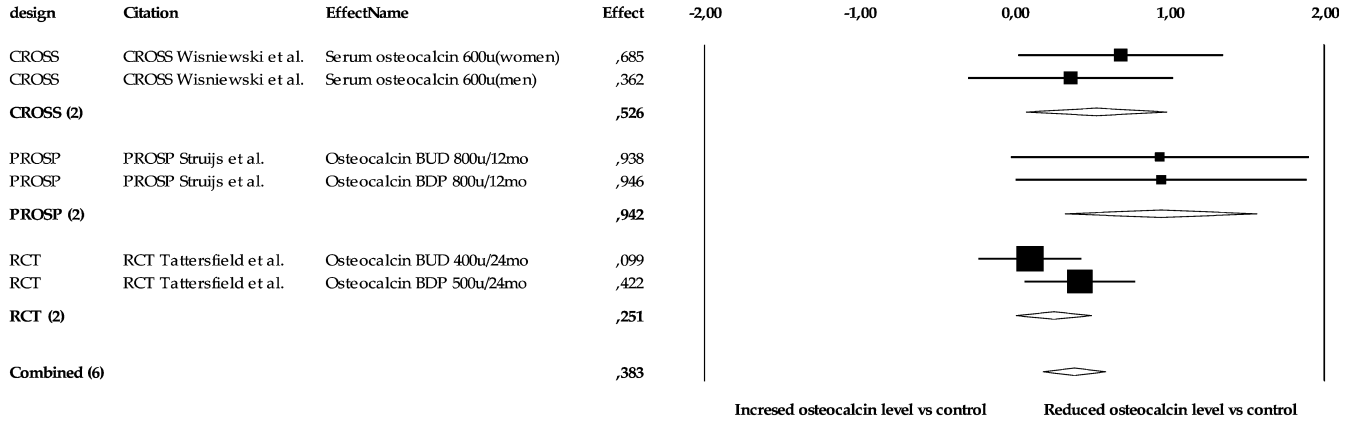

Fig. 6 ICS effects on osteocalcin level

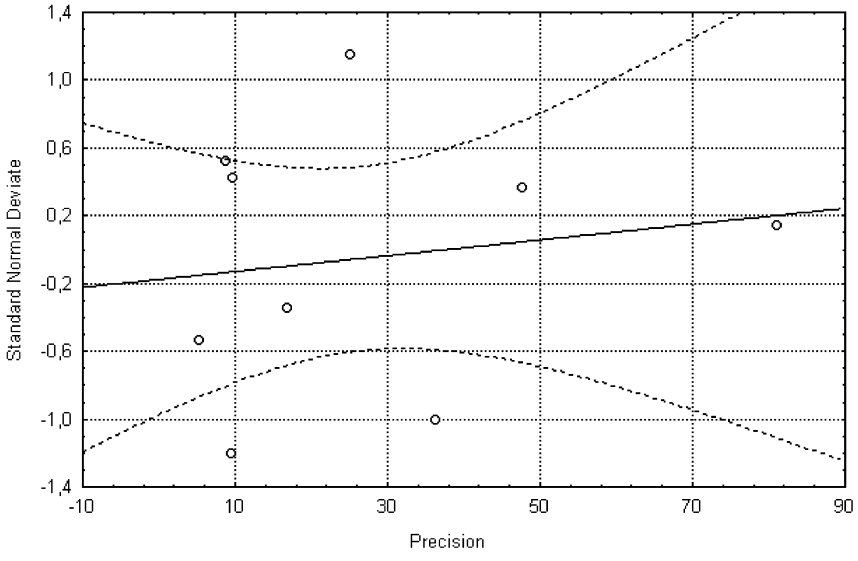

Fig. 7 Publication biais investigation

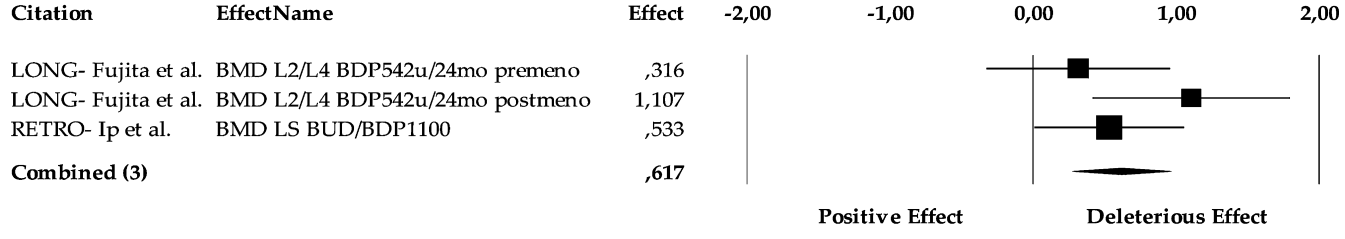

Fig. 8 BMD LS assessment in studies comparing patients on ICD and healthy controls

and inhaled corticosteroids as a risk factor for osteoporosis, the probability of fracture when exposed to ICS was difficult to assess clearly, keeping in mind the potential confounding factors for each relation; therefore, with respect to the time course of inhaled-corticosteroids-induced osteoporotic fractures, trials of 3 years were too short to reach statistical significance. Furthermore, few studies assessed the pragmatic intake of ICS, i.e. there could have been periods free of ICS intake during the follow-up periods; however, the study by Van Staa et al. [20] with a mean follow-up of 292,102 person years in the ICS group provided a significantly increased risk for hip fracture and a dose-response relationship. The control group used for this analysis was "bronchodilator users" instead of healthy patients and we considered the subgroup analysis of patients taking a standardized daily dose of 700 μg or more BDP, the mean dose in other studies being 704 μg. It was of interest to note that, in that analysis, relative risks were all significantly increased, except for forearm fracture, when comparing patients exposed to ICS and controls.

Urinary deoxypyridinoline, pyridinoline and ICTP levels, three markers of bone resorption, were not affected, both in prospective and retrospective studies,

whereas PICP, BALP and osteocalcin, three markers of bone formation, were significantly decreased. This is an important observation in agreement with most recent data suggesting that glucocorticoids act predominantly as inhibitors of bone formation [37]. We found no trial including osteoprotegerin as an outcome. Sasaki et al. [38] reported this recently identified cytokine to be an inhibitor of differentiation and activation of osteoclast, significantly decreased after short-term administration of glucocorticoid. Further studies are needed to assess its usefulness in monitoring bone status among ICS users.

We compared these primary results with data from controlled studies on healthy patients exposed to ICS or not, and on studies using healthy controls. Reid et al. [39] and Riancho et al. [40] found no decrease in BMD among asthma and COPD patients, whereas Praet et al. [41] reported a significant one. Fujita et al. [27] found a significant decrease in intact osteocalcin level and L2–L4 BMD in early postmenopausal women compared with healthy controls, an observation not reported for premenopausal women. Herrala et al. [28] provided results with marked heterogeneity between groups at baseline and therefore their data were not taken into account. Luengo et al. [30] reported no intergroup effect of budesonide or beclomethasone on BMD after 1 year. Ip et al. [32] found reduced BMD at all sites. Leech et al. [26] reported a decreased level of osteocalcin in a healthy group of patients allocated to ICS and compared to controls after only 2 weeks. Toogood et al. [23] and Hodsman et al. [24] found similar results. When combining the results of the controlled trials on lumbar spine density in studies in which patients allocated to ICS were compared with healthy subjects, we found a significant effect for both premenopausal and postmenopausal patients (ES = 0.617, $p = 0.001$; Fig 8). Considering all the elements above, osteocalcin level, as well as BMD, appeared to be reduced both in healthy subjects allocated to ICS and asthmatic ones, especially in postmenopausal women.

We explored the variability of effects among BUD, BDP and TCA on femoral neck/hip and on lumbar spine BMD. The mean BUD dose (SD) was 686 μg/day (158 μg/day), BDP 703 μg/day (123 μg/day) and TRI 1000 μg/day (282 μg/day). Budesonide appeared to be the ICS leading to the smallest bone loss, followed by beclomethasone and triamcinolone; however, TCA was investigated on a 3-year basis, whereas the mean duration for BUD and BDP trials was only 18 months. These findings are highly consistent with the rates of BMD decline found in the regression analysis (BUD: −0.010; BDP: −0.016; TCA: −0.028). If we admit a linear bone loss in glucocorticoid-induced osteoporosis, a patient exposed to TCA at a dose of 1 mg/day during 20 years would thus experience a 6.7% decrease in BMD compared with unexposed asthma or COPD control, whereas the related loss for BUD would be 2.4%. Despite this, these assumptions are to be cautiously considered, since a multivaried analysis of pooled raw data from each study is needed to properly appraise this issue.

Another critical point is the role of the underlying diseases in the process of bone loss, independently of the drug used. We investigated whether being asthmatic, COPD patient or healthy control would result in different effects of inhaled ICS on BMD by performing separate meta-analyses including distinctively controlled trials on healthy patients or studies in which asthmatic patients on ICS were compared with healthy subjects. The effects of ICS were comparable to the primary analysis effects. The ICS played a significant role in the bone loss process regardless of the underlying disease. This effect being three times higher than our corresponding results for asthma or COPD patients, it might be possible that the time–effect model might not be linear, e.g. compensatory mechanisms take place in patients exposed to ICS on a long-term basis. This hypothesis has to be confirmed in future.

Conclusion

The results of our study might have practical implications in the long-term management of asthma and COPD. All considered inhaled corticosteroids, when compared with placebo or controls in studies of high methodological quality, appear to affect bone metabolism in adults and, as a consequence, markers and BMD, in asthma, COPD or in healthy adults. Triamcinolone led to the most deleterious effect, followed by beclomethasone and budesonide. These findings suggest that bone density should be carefully monitored in pre- and postmenopausal women taking inhaled glucocorticoids, and that the lowest inhaled corticosteroid dose that control symptoms should be given.

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