Inhaled corticosteroids and the risk of fractures in older adults: a systematic review and meta-analysis
Etminan M, Sadatsafavi M, Ganjizadeh Zavareh S, Takkouche B, FitzGerald JM

CRD summary
The authors concluded that there was no association between use of inhaled corticosteroids and fractures in older adults. They found a slight increase in risk associated with high-dose inhaled corticosteroids, but considered this not to be clinically significant. The authors' conclusions appeared to reflect the evidence presented, but their reliability was unclear due to the uncertain quality of the included studies.

Authors' objectives
To evaluate the risk of fractures among older adults treated with inhaled corticosteroids (ICS).

Searching
MEDLINE, EMBASE, The Cochrane Library and ISI Proceedings were searched to August 2007 for published articles in any language; search terms were reported. LILACS database was searched. Reference lists of retrieved articles and reviews were scanned for additional studies.

Study selection
Eligible studies were clinical trials, case-control and cohort studies which explicitly described exposure to inhaled corticosteroids in older adults (aged more than 40 years), reported explicitly defined outcomes (largely fractures), provided data on relative risks (RR) or odds ratios (OR) or enough data to enable calculation and controlled for confounding using statistical adjustment or matching within the study design.

Half of the included studies included participants with chronic obstructive pulmonary disease (COPD); other studies, where reported, included patients with other respiratory diseases. Mean age of participants ranged from 43 years to 81 years. The included studies were conducted in Europe, USA and Canada.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted and used to calculate risk ratios and 95% confidence intervals (CIs).

It appeared that data were extracted by two reviewers and disagreements were resolved through discussion.

Methods of synthesis
Risk ratios were pooled using a random effects model. Where information was lacking on the risk of any fracture, or where risks were reported for different age groups and not the whole population, risks across specific fracture sites and age groups were combined using a fixed-effects model to obtain the summary rates for any fractures. Subgroup analyses were conducted and included setting, dose response (high dose compared to low dose), patient category (COPD compared to general population) and study design. Heterogeneity was assessed using the Q statistic. Sensitivity analyses were conducted to explore reasons for heterogeneity. Publication bias was assessed by visual inspection of funnel plots.

Results of the review
Thirteen studies were included in the review (number of participants not reported): four randomised controlled trials (RCTs), three cohort studies and six case-control studies.
There was no evidence of an increased risk of any fracture for patients treated with inhaled corticosteroids (RR 1.02, 95% CI 0.96 to 1.08; 13 studies). Subgroup analyses reported an increased risk of any fractures among high-dose inhaled corticosteroid participants compared to control (RR 1.30, 95% CI 1.07 to 1.58); there was no increased risk related to subgroup analyses of setting or study. There was evidence of statistical heterogeneity for some analyses, but there were no significant changes to the results when studies responsible for heterogeneity were removed from these analyses.

There was evidence of a reduced risk of hip fractures for patients treated with inhaled corticosteroids (RR 0.91, 95% CI 0.87 to 0.96; six studies), but no evidence of increased risk for hip fractures in community settings, COPD patients or high-dose inhaled corticosteroid users. There was some evidence of statistical heterogeneity for the subgroup analysis of setting, but when studies responsible for heterogeneity were removed there was no significant change to the result.

There was no evidence of publication bias.

Authors' conclusions
There was no association between use of inhaled corticosteroids and fractures in older adults. A slight increase in risk was seen in those who used high-dose inhaled corticosteroids, but this was probably not clinically significant. The association between use of inhaled corticosteroids and fractures should be evaluated further in future studies.

CRD commentary
The review question was clear with reasonable inclusion criteria. Several relevant sources were searched. Attempts were made to reduce language bias. Only published studies were included and so there was potential for publication bias, but formal assessment found no evidence of this. It appeared that appropriate methods to reduce reviewer error and bias were used for study selection and data extraction. Study validity was not assessed and so it was not possible to comment on the reliability of the results presented. It should be noted that (as the authors stated) most of the studies were observational (a type of study design that is subject to multiple biases). No details were reported of the treatment regimen for inhaled corticosteroid treatment in the included studies; therefore, it was difficult to assess the generalisability of the results. Although the authors pooled data from studies of different designs, subgroup analyses included analyses limited to RCTs; however, numbers of participants in individual studies and analyses were not reported and so it was not possible to judge whether analyses were likely to be adequately powered to detect an increased fracture risk in inhaled corticosteroid users. Duration of exposure to inhaled corticosteroids was not reported and this too limited the strength of the evidence (a short exposure may not be sufficient to increase risk). One author received fees or has membership of panels sponsored by manufacturers of asthma-related drugs.

The authors' conclusions appeared to reflect the evidence presented, but their reliability was unclear due to uncertain quality of the included studies, insufficient details of included studies and evidence based predominantly on observational studies.

Funding
CIBER en Epidemiologia y Salud Publica (CIBER-ESP), Spain.

Bibliographic details

PubMedID
18422381

Original Paper URL

Indexing Status
Subject indexing assigned by NLM
MeSH
Administration, Inhalation; Adrenal Cortex Hormones /administration & dosage /adverse effects; Aged; Aged, 80 and over; Dose-Response Relationship, Drug; Female; Fractures, Bone /epidemiology; Hip Fractures /epidemiology; Humans; Male; Middle Aged; Randomized Controlled Trials as Topic; Risk

AccessionNumber
12008106133

Date bibliographic record published
15/04/2009

Date abstract record published
09/02/2011

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.