Thiazide diuretics and fractures: can meta-analysis help?

Jones G, Nguyen T, Sambrook P N, Eisman J A

Authors' objectives
To explore whether duration and/or dose of thiazide diuretics has an effect on osteoporotic fracture.

Searching
MEDLINE and Excerpta Medica were searched for English language studies using the search terms 'thiazide' and 'fracture', and 'diuretic' and 'fracture'. The period searched is not stated but the search was performed by a professional librarian in November 1993. The database search was supplemented by referring to textbooks, reviews and back-references, and by a second search using the terms 'thiazide' and 'bone mineral density'.

Study selection
Study designs of evaluations included in the review
Published cohort and case-control studies.

Specific interventions included in the review
Thiazide.

Participants included in the review
Males and females with mean ages ranging from 50 to 83.

Outcomes assessed in the review
The risk of osteoporotic fracture.

How were decisions on the relevance of primary studies made?
The authors do not state how the studies were selected for the review, or how many reviewers performed the selection. [A: Inclusion criteria were applied by a single author.]

Assessment of study quality
Representativeness of fracture subjects; adequacy of fracture definition; selection of controls or selection of non-thiazide using cohort; definition of controls or adequacy of fracture exclusion in cohort studies; comparability of cases and controls or cohorts; ascertainment of thiazide exposure; thiazide usage ascertained by some method in cases and controls or cohorts. One author, blind to study outcome and the method of data extraction, assessed study quality.

Data extraction
[A: By a single author on two separate occasions two weeks apart. Discrepancies were resolved by reference to the original papers]

Methods of synthesis
How were the studies combined?
The studies were pooled in a meta-analysis using the method of Fleiss, which weights studies according to the inverse of the 95% confidence interval. Where significant heterogeneity was observed, the fixed-effect model was substituted by a random-effects model. A funnel plot was also performed to test for publication bias.

How were differences between studies investigated?
Chi-squared analysis was used to test for heterogeneity.
Results of the review
Thirteen studies providing data on 29,600 patients (2 cohort studies and 11 case control studies).

Protection against Hip Fracture:
Current thiazide users (duration of use of at least the previous 6 months) OR=0.82 (95% CI: 0.73, 0.91).
Long-term thiazide users OR=0.82 (95% CI: 0.62, 1.08).
Short-term users OR=1.23 (95% CI: 0.99, 1.54).

Authors' conclusions
Current thiazide users have a 20% reduction in fracture risk and that long-term use may reduce fractures by a similar amount. In the absence of suitable randomised controlled trials thiazides should be considered as part of an approach to osteoporotic fracture prevention, particularly in hypertensive subjects.

CRD commentary
A clearly-written and well-structured article. The authors have reported sufficient methodological details to meet the selection criteria for DARE. However, it is not stated how the inclusion criteria were applied, nor how the data were extracted. The search is well-described and was not restricted to MEDLINE, a frequent flaw of many reviews. However, there are other databases available that may have contained studies not cited in the two databases searched (e.g. CINAHL and Current Contents), and the restriction of the search to studies only published in the English language could be criticised. On the data presented, the authors' conclusion for current and short-term use appears valid, but the statement that long-term use is likely to be effective is not supported. The odds ratio is not significant and it should not be inferred that the direction of effectiveness favours thiazide, considering the design flaws of the primary studies; a meta-analysis of observational studies can be misleading.

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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.