The role of vitamin D in corticosteroid-induced osteoporosis: a meta-analytic approach
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Authors' objectives
To determine if vitamin D is more effective than no therapy of calcium alone in the management of corticosteroid-induced osteoporosis, and to determine how vitamin D compares with other osteoporosis therapies, e.g. bisphosphonates, calcitonin, or fluoride.

Searching
MEDLINE (1966-Dec 1997) and Current Contents (Oct 1997-Jan 1998) were searched (search strategy reported). Additional studies were located through searching the bibliographies of retrieved articles, and abstracts from national meetings of the ACR (1986-1997), the American Society for Bone and Mineral Research (1990-1997), and the Endocrine Society (1990-1996), as well as the European Symposium on Calcified Tissue meetings XIX-XXIV (1986-1997). Content experts and pharmaceutical companies were also contacted for information about other published and unpublished work. Only English or French language studies were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) lasting at least 6 months. The studies reported in the review had follow-up periods ranging from 6 to 24 months. Studies were defined as studies of prevention if the intervention was started within the first 6 months of starting corticosteroid therapy. Studies that randomised participants using alternate allocation to treatment were excluded.

Specific interventions included in the review
In the first meta-analysis vitamin D plus calcium, or vitamin D alone, were compared against no therapy, placebo or calcium alone. In the second meta-analysis vitamin D plus calcium, or vitamin D alone, were compared against bisphosphonates (e.g. alendronate, etidronate), calcitonin, fluoride (e.g. disodium mono-fluorophosphate, sodium fluoride) or hormone replacement therapy, with or without vitamin D or calcium. In all cases vitamin D included any of its metabolites or analogs, e.g. calcitriol, alfacalcidol, dihydrotachysterol. The dose regimens of vitamin D varied in terms of the frequency and size of doses. Doses regimens of the other intervention and control treatments were not stated.

Participants included in the review
Patients receiving oral corticosteroid therapy, including adults and children. Participants reported in the review included patients suffering from juvenile rheumatoid arthritis, rheumatoid arthritis, asthma, systemic lupus erythematosus, mixed connective tissue disease, polymyalgia rheumatica/giant cell arteritis, polymyositis/dermatomyositis, multiple sclerosis, vasculitis and transplant patients.

Outcomes assessed in the review
Change at 12 months in bone mineral density (BMD) of lumbar spine (LS). BMD had to be evaluated using dual x-ray absorptiometry (DXA), dual-photon absorptiometry (DPA), or quantitative computed tomography. If 12-month data were not available then the following time points were used in order of preference: 6 months and 24 months. Fracture incidence was used as a secondary outcome. Studies were excluded if they did not report the mean percent or actual change in BMD in each study arm, along with an associated measure of variability (standard deviation, standard error, 95% confidence interval (CI), or exact P).

How were decisions on the relevance of primary studies made?
Studies were assessed in a blinded manner using a coded sheet. All references to the authors, site of study, journal and year of publication were removed. The methods and results sections were assessed separately. Two rheumatologists each reviewed the methods section and a statistician reviewed the results section. Disagreements in the assessment of the methods sections were resolved through adjudication.
Assessment of study quality
The authors do not report a method for assessing validity. Not stated. However, the authors performed sensitivity analyses according to the quality of the studies as judged by publication in a peer-reviewed journal, double-blinding and the use of an intention-to-treat analyses. The quality of individual studies based on these three criteria was not reported.

Data extraction
A standardised form was used and if necessary means and measures of dispersion were approximated from figures in the manuscripts. Authors were contacted for additional information. It is not stated how many reviewers were involved in the data extraction process. Tables reported in the review include the following types of data: study details, number of participants at follow-up, patient details, intervention and control details, method of BMD evaluation, duration of follow-up, % change in LS BMD for each study group, and the effect size. The effect size or standardised mean difference was calculated for each trial (i.e. the difference in mean percent change in BMD, between the treatment and control arms of the trial, divided by the standard deviation of the mean percent change of the control arm). If necessary the actual change in BMD was used to calculate the effect size. To reduce bias, all of the effect sizes were multiplied by a correction factor that depended on the sample size. The effect size of treatment on fracture incidence was also calculated for each study using dichotomous data, as described by Whitehead and Whitehead (See Other Publications of Related Interest no.1).

Methods of synthesis
How were the studies combined?
For meta-analysis 1, treatment effects of studies comparing vitamin D plus calcium versus no therapy or calcium alone were pooled for each outcome using a random-effects model. In order to provide a better sense of the clinical magnitude of the pooled effect sizes for the BMD outcome the data were converted into treatment difference by multiplying the effect size by a pooled estimate of standard deviation from the control arms in the analysis. For the incidence of fractures the effect sizes were reconverted into odds ratios (ORs) from log Ors.

For meta-analysis 2, similar methods to meta-analysis 1 were used. Treatment effect sizes were pooled for each of the different types of osteoporosis therapies (bisphosphonates, calcitonin, fluoride and hormone replacement therapy) against vitamin D alone and vitamin D with and without calcium. To avoid the problem of correlated effect sizes where studies had three or more arms comparing different dosages of the same drug with a control arm, only the treatment arm with the most commonly prescribed dosage was used. In both meta-analyses 95% CIs were reported and the possibility of publication bias was investigated using regression analysis. In meta-analysis 2 only BMD was investigated as too few studies provided information on fractures.

How were differences between studies investigated?
A Q statistic was used (level of significance P<0.05.). Sensitivity analyses according to study quality were performed; as were sub-group analyses according to the control group (no therapy versus calcium alone), whether an active metabolite or analog of vitamin D was used and the time of the initiation of therapy (prevention versus treatment).

Results of the review
A total of 21 RCTs (11 in meta-analysis 1 and 12 in meta-analysis 2), providing 23 comparisons, and including 1260 participants in total (at follow-up).

Meta-analysis 1.

Included nine comparisons of vitamin D plus calcium versus no therapy/placebo (n=4) or calcium alone/calcium plus placebo (n=5). Two studies used in the sensitivity analyses compared vitamin D alone with either no therapy or calcium alone. One of the studies was a paediatric study and six studies were defined as prevention studies. No statistical heterogeneity was reported between any of the comparisons (P=0.14) and there was no evidence of publication bias (P=0.32). Pooled effect sizes for LS BMD: 1. Vitamin D plus calcium versus no therapy or calcium alone (n=9) 0.60; 95% CI: 0.34, 0.85, P<0.0001 (equivalent to a 3.2% difference in the % change in BMD between treatment and
control, in favour of vitamin D plus calcium treatment)

2. Including two studies using vitamin D alone (n=11) 0.57; 95% CI: 0.36, 0.78, P<0.0001. Effect size was not affected by removing the paediatric study (n=8).

4. Only peer-reviewed published articles (n=7) 0.59 (95% CI: 0.32, 0.85, P<0.0001).

5. Findings remained similar when studies were excluded that were not double-blinded (n=not stated) or that did not provide intention-to-treat results (n=not stated).

6. Vitamin D plus calcium versus no therapy/placebo (n=4) 0.66; 95% CI: 0.35, 0.97, P<0.0001.

7. Vitamin D plus calcium versus calcium alone or with placebo (n=5) 0.57; 95% CI: 0.13, 0.96, P=0.009.

8. Activated metabolites/analogs versus placebo/calcium alone (n=4) 0.43; 95% CI: 0.04, 0.82, P=0.03.

9. Non-active vitamin D versus placebo/calcium alone (n=5) 0.74; 95% CI: 0.42, 1.06, P<0.0001.

10. Prevention studies only (n=5) 0.62; 95% CI: 0.34, 0.89, P=0.0001.

11. Non-prevention studies only (n=4) 0.53; 95% CI: -0.08, 1.13, p=0.09.

Pooled effect sizes for fracture incidence:

12. Fracture reduction (n=3) -0.89; 95% CI: -1.90, 0.12, P=0.08 (equivalent to OR=0.41; 95% CI: 0.15, 1.13).

Meta-analysis 2.

Included 12 comparisons, six were with bisphosphonates, four with calcitonin and two with fluoride (none were with hormone replacement therapies). In one of the studies comparing fluoride, vitamin D was provided to patients in both arms if they had low serum levels of 25-hydroxyvitamin D. There was statistical heterogeneity among the bisphosphonate studies (P=0.003), but not among the calcitonin (P=0.12) studies. There was no evidence of publication bias for either bisphosphonate (P=0.60) or calcitonin (P=0.12) studies. There were insufficient fluoride studies (n=2) to make a comment about heterogeneity or publication bias.

Pooled effect sizes for LS BMD:

1. Bisphosphonates versus vitamin D (n=6) 0.57; 95% CI: 0.09, 1.05, P=0.02 (equivalent to a 2.0% difference in the % change in BMD in favour of bisphosphonate therapy).

2. Calcitonin versus vitamin D (n=4) 0.03; 95% CI: -0.39, 0.45, P=0.90.

3. Fluoride versus vitamin D (n=2) 0.66; 95% CI: 0.11, 1.22, P=0.02.

4. Excluding the study in which all participants could received vitamin D 0.88; 95% CI: -0.28, 2.04.

Authors’ conclusions

Vitamin D plus calcium is superior to no therapy or calcium alone in the management of corticosteroid-induced osteoporosis. Vitamin D is less effective than some osteoporosis therapies. Based on the findings vitamin D compounds that are activated and those that are not, are both effective in the management of corticosteroid-induced osteoporosis.

CRD commentary

This is a clearly reported review with a well-defined review question. The methodological details of the review are reported (e.g. the methods of study selection and data extraction, and the number of reviewers involved in study selection) in most cases. However, it is not clear how many reviewers were involved in extracting data or whether any
formal assessment of study validity was performed. The literature search was extensive and sought to locate both unpublished and published work. The authors also assessed the possible effects of publication bias. However, by limiting the literature searches to only those articles written in English or French, relevant data may have been missed.

Before pooling the data study heterogeneity was statistically assessed and where possible sensitivity and sub-group analyses were performed. However, the authors still report data from the pooling of studies where significant heterogeneity was reported (i.e. bisphosphonate studies). Taking all of these comments into consideration it would appear that the authors' findings are supported by the results presented, except in cases where studies were pooled in the presence of heterogeneity.

**Implications of the review for practice and research**

**Practice:** The authors stated that 'treatment with vitamin D plus calcium, as a minimum should be recommended to patients receiving long-term corticosteroids'. However, the authors also stated that 'when prescribing any formulation of vitamin D, the safest and lowest effective dosage should be used, accompanied by appropriate monitoring for vitamin D intoxication'.

**Research:** The authors did not state any implications for further research.

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Record Status
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