Effect of vitamin D on blood pressure: a systematic review and meta-analysis

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CRD summary
This review concluded that there was weak evidence to support a small effect of vitamin D on blood pressure in studies of hypertensive patients. Although this was generally a well-conducted review, the lack of high-quality trials, the small sample sizes and variability across studies made the reliability of the authors’ conclusions unclear.

Authors' objectives
To examine whether vitamin D supplementation reduces blood pressure.

Searching
MEDLINE, EMBASE, CINAHL and The Cochrane library were searched without language restrictions from inception to June 2008; search terms were reported. Google and controlled-trials.com were searched for unpublished literature and trials. Additional studies were sought through handsearches of included studies and previous reviews.

Study selection
Randomised controlled trials (RCTs) that compared a vitamin D regimen with placebo were eligible for inclusion. Interventions, for any duration, included activated vitamin D, unactivated vitamin D2 and D3 and ultraviolet B radiation. Cointerventions such as calcium in both arms were permitted, but studies where combination therapy was compared with placebo were excluded. Follow-up data had to be available at least one week following dosing. Eligible outcomes comprised changes in: blood pressure (systolic and diastolic, office or ambulatory); endothelial function or measures of arterial stiffness; left-ventricular mass, volume and function; lipid profile; all-cause mortality, including cardiovascular mortality; morbidity including new onset diabetes mellitus; blood glucose control; cardiovascular diseases; and adverse events.

Mean age, where stated, ranged from 48 to 75 years of age. Participants included healthy individuals, elderly people and those with impaired glucose intolerance (including diabetes). All studies were conducted in community settings in Europe, except for a study of institutionalised patients in Taiwan; a small number of single-sex studies were included. For most studies participants were hypertensive at baseline. In just over one quarter of studies participants were normotensive. In hypertensive studies systolic blood pressure ranged from 141 to 157 and diastolic blood pressure ranged from 81 to 99. Interventions included alphacalcidiol, cholecalciferol, ergocalciferol and ultraviolet A and ultraviolet B.

Two reviewers independently selected studies for inclusion in the review.

Assessment of study quality
Two reviewers independently assessed study quality using the criteria: baseline characteristics comparable between groups; allocation concealment; blinding; description of dropouts; and intention-to-treat analysis. Each criterion was rated as adequate, inadequate or unable to assess. Disagreements were resolved through consensus.

Data extraction
Two reviewers independently extracted data for mean changes from baseline for the outcomes of interest. Where standard deviation of the change in blood pressure was not reported or could not be calculated from the 95% confidence interval (CI), it was imputed as the average of the standard deviation of initial and follow-up blood pressure; where standard deviations were not reported these were calculated from the remaining studies as mean standard deviation of change. Disagreements were resolved through consensus.

Methods of synthesis
Weighted mean differences (WMDs) and their 95% CI, were pooled using a fixed-effect model. A random-effects model was used if significant heterogeneity was present. Heterogeneity was assessed using the I² test (significant
heterogeneity defined as >50%). Subgroup analyses were undertaken for studies with a mean systolic blood pressure of more than 140mmHg, a diastolic blood pressure of more than 90mmHg or mean arterial pressure more than 105mmHg. Publication bias was assessed using a funnel plot.

**Results of the review**

Eleven RCTs were included in the review (n=716, range 18 to 145). Studies were small and of variable methodological quality. Random allocation was reported for all studies, but it was not possible to assess whether adequate allocation concealment was undertaken for most. Eight studies provided reasons for withdrawal together with numbers of dropouts. One study undertook intention-to-treat analyses. Groups were well balanced in seven studies. Nine studies mentioned blinding and the procedures were described in five. Duration of treatment varied from five weeks to 12 months. There was no evidence of publication bias for hypertensive studies.

**Hypertensive studies:** There was a non-significant reduction in systolic blood pressure in the vitamin D group compared with placebo (WMD -3.6mmHg, 95% CI -8.0 to 0.7; eight studies). A small statistically significant reduction was observed for diastolic blood pressure (WMD -3.1mmHg, 95% CI -5.5 to -0.6; eight studies). Significant heterogeneity was present between studies for these comparisons.

There was a significant reduction in systolic blood pressure with unactivated vitamin D (WMD -6.2mmHg, 95% CI -12.3 to -0.04) compared with a non-significant decrease in the activated vitamin D group (WMD 0.7mmHg, 95% CI -4.8 to 6.2). There were no significant reductions for diastolic blood pressure for either activated or unactivated vitamin D. Significant heterogeneity was present between studies for these comparisons.

**Normotensive studies:** No reduction in blood pressure was seen in studies that examined patients who were normotensive at baseline (three studies).

**Authors' conclusions**

There was weak evidence to support a small effect of vitamin D on blood pressure in studies of hypertensive patients.

**CRD commentary**

The review addressed a clear question and was supported by appropriate inclusion criteria. Several relevant sources were searched without language restrictions and appropriate attempts were made to locate unpublished studies. Study selection, data extraction and quality assessment were performed in duplicate, which reduced risks of error and bias. There was an appropriate assessment of the quality of the included studies; studies were of variable quality and most had small sample sizes (<60 patients). The absence of reported quality results on a study-by-study basis represented a limitation when interpreting the reliability of the review findings. The synthesis using meta-analysis appeared appropriate and an assessment of heterogeneity was undertaken. Subgroup analyses were conducted in an attempt to investigate heterogeneity. Although this was generally a well-conducted review, the lack of high-quality trials, the small sample sizes and variability across studies made the reliability of the authors' conclusions unclear.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further large RCTs were required to define the optimum dose, dosing interval and type of vitamin D as well as studies to assess the magnitude of the effect of vitamin D on blood pressure reduction (especially in patients with hypertension) and the impact upon cardiovascular events and death.

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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.