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

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Objectives **Vitamin D insufficiency has been linked to hypertension and cardiovascular events in observational studies. It is unclear whether vitamin D supplementation can reduce blood pressure, and, if so, by how much.**

Methods **We performed a systematic review and meta-analysis to examine whether vitamin D reduces blood pressure. Databases including MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature and the Cochrane library were searched, supplemented by searches of grey literature, unpublished trials and references from included studies. Studies were assessed by two reviewers independently according to a prespecified protocol. Interventions included activated vitamin D, unactivated vitamin D2 and D3 and ultraviolet B radiation.**

Results **Eleven randomized, controlled trials fulfilled the inclusion criteria. Studies were small and of variable methodological quality. Mean baseline blood pressure was more than 140/90 mmHg in eight studies. Meta-analysis of these eight studies showed a nonsignificant reduction in systolic blood pressure in the vitamin D group compared with placebo [−3.6 mmHg, 95% confidence interval (CI) −8.0 to 0.7]. A small, statistically significant reduction was seen in diastolic blood pressure (−3.1 mmHg, 95% CI −5.5 to −0.6). Subgroup analysis suggested that unactivated vitamin D produced a greater fall in systolic blood pressure than activated vitamin D (−6.2 mmHg, 95% CI −12.32 to −0.04, vs. +0.7 mmHg, 95% CI −4.8 to 6.2). No reduction in blood pressure was seen in studies examining patients who were normotensive at baseline.**

Conclusion **We found weak evidence to support a small effect of vitamin D on blood pressure in studies of hypertensive patients.** ***J Hypertens*** **27:1948–1954 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: blood pressure, hypertension, systematic review, vitamin D

Abbreviations: 1,25OHD, 1,25dihydroxyvitamin D; 25OHD, 25 hydroxy vitamin D; Ca++, calcium; CI, confidence interval; DBP, diastolic blood pressure; MAP, mean arterial pressure; PTH, parathyroid hormone; SBP, systolic blood pressure; UVA, ultraviolet A; UVB, ultraviolet B

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Introduction

Vitamin D insufficiency is common [1,2], especially in populations living at temperate latitudes. Vitamin D has been known to regulate calcium and bone homeostasis for many decades, but recent investigations have revealed that vitamin D receptors exist on a very wide range of tissues, including the endothelium and the myocardium, suggesting a much wider range of biological functions for vitamin D. Of particular cardiovascular interest are the observations that vitamin D can suppress renin production via effects on the juxtaglomerular apparatus [3] and the fact that endothelial cells contain vitamin D receptors, thus providing a direct vascular substrate for vitamin D to exert effects [4]. Furthermore, vitamin D is known to suppress parathyroid hormone (PTH) production, itself associated with cardiovascular disease, and can suppress pro-inflammatory cytokine production, including tumour necrosis factor (TNF)-alpha [5], which has been implicated in the promotion of arterial stiffness. There are, therefore, several possible pathophysiological pathways by which vitamin D could exert antihypertensive and vasculoprotective effects.

Observational data suggest that low 25 hydroxyvitamin D levels are associated with higher blood pressure, with a greater chance of developing hypertension in the future [2,6], and with increased mortality rates and higher rates of cardiovascular events [7,8]. Patients with hypertension and low vitamin D levels appear to be at particular risk of cardiovascular events [9]. Although most interventional studies using vitamin D have focused on falls and fractures as their primary endpoint [10,11], at least one meta-analysis of interventional studies suggests that vitamin D supplementation may reduce total mortality [12]. The effects of calcium on blood pressure reduction have recently been systematically reviewed [13]; however, a systematic review of the effects of vitamin D supplementation on blood pressure reduction has not previously been published. Thus, in order to ascertain the size of any effect on blood pressure, to examine which patient

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groups might benefit and to gain insight into which interventions were effective, we systematically reviewed the literature for randomized controlled trials of vitamin D supplementation to reduce blood pressure.

Methods

Search strategy

We conducted a systematic review, based on a prespecified protocol, which was devised according to the guidelines of the Cochrane Collaboration. Eligible trials had to fulfil the following criteria to be included in this analysis: trials had to be of randomized controlled design, comparison of regimen based on vitamin D with placebo (cointerventions such as calcium in both arms was permitted, but combination therapy vs. placebo was excluded as we wished to isolate the effect of vitamin D alone). Evaluation of blood pressure reduction or cardiac risk factor modification was the main aim of the study. No language restrictions were imposed. We included studies that used ultraviolet light to produce an increase in vitamin D level.

Data source and study search

We searched MEDLINE, EMBASE, the Cochrane database and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), from earliest date 1966 until June 2008. Grey literature was sought using Google, and unpublished trials were sought using www.controlled-trials.com. Search terms used were vitamin D, vitamin D3, vitamin D2, cholecalciferol, ergocalciferol, alphacalcidol, alfacalcidol, paricalcitol and doxercalciferol combined with blood pressure, hypertension, cardiovascular, mortality, randomized controlled trials or placebo. In addition, we handsearched reference list of original studies and previous review articles to identify other potentially eligible studies.

Intervention classification

Vitamin D2 (ergocalciferol), vitamin D3 (cholecalciferol), 1,25 dihydroxycholecalciferol (calcitriol), 1-alpha calcidiol, paricalcitol, doxercalciferol and ultraviolet B (UVB) radiation were considered as interventions. The interventions for any duration were included in which follow-up data were available at least 1 week after dosing. 1-Alpha hydroxylated preparations (calcitriol, 1-alpha calcidiol, doxercalciferol and paricalcitol) were considered to be 'activated' preparations, as they did not require 1-alpha hydroxylation *in vivo* to reach their active pharmacological form.

Outcomes

Outcomes of interest were change in office or ambulatory blood pressure (systolic and diastolic), change in endothelial function or measures of arterial stiffness, change in left ventricular mass, volume and function, change in lipid profile, all-cause mortality including cardiovascular mortality, morbidity including new onset diabetes mellitus, blood glucose control, cardiovascular diseases and other adverse events. We also collected data on age, sex, dwelling place, disease state, geographical location and source of trial funding.

Data extraction and quality assessment

Data were abstracted by two reviewers (M.D.W. and M.A.N.) independently using a standard proforma, and discrepancies were resolved by consensus. In cases in which standard deviation of the change in blood pressure was not reported or could not be calculated from 95% confidence interval (CI), we imputed this as the average of standard deviation of initial and follow-up blood pressure [14]. If no standard deviation was reported, we used the mean standard deviation of change from all the remaining studies. Study quality was assessed by two reviewers (M.D.W. and M.A.N.) independently, and discrepancies were resolved by consensus. Allocation concealment, blinding, baseline comparability of groups, description of drop outs and availability of intention to treat analysis were categorized as adequate, inadequate or unable to assess.

Data analysis and synthesis

Meta-analysis was undertaken in cases in which results could be combined quantitatively using *Rev Man 4.2* software (Cochrane Collaboration). I^2 tests for heterogeneity across analyses were performed and possible sources of heterogeneity explored. Fixed models were used if heterogeneity was less than 50%, otherwise random effect models were used. For subgroup analyses, we defined the hypertensive subgroup as those with mean baseline study blood pressure of more than 140 mmHg systolic, more than 90 mmHg diastolic or more than 105 mmHg for mean arterial pressure (MAP).

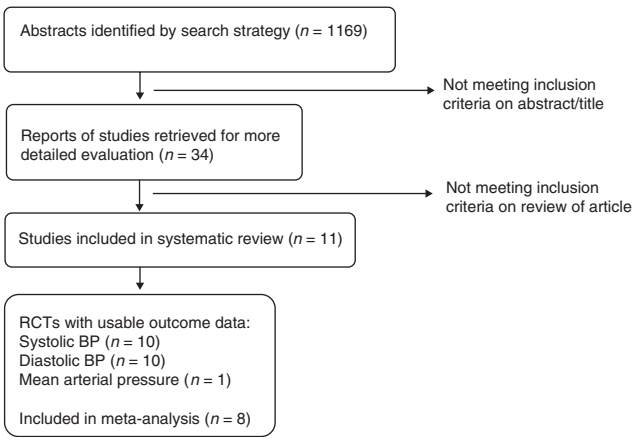
Results

Selection of trials

Abstracts (1169) were found by the initial search strategy. Examination of the abstracts identified 34 articles for detailed evaluation. Twenty-three studies did not meet inclusion criteria and hence were excluded. Details are given in Fig. 1. The reasons included nonrandomized trial, absence of control group, calcium supplementation in intervention group only or cardiovascular parameters not the primary reason for the study. Eleven studies were finally included which reported the effect of intervention on blood pressure. Study details are given in Table 1 [4,5,15–23]; interventions and effects on blood pressure are given in Table 2 [4,5,15–23].

All studies were conducted in western Europe and included participants from the community apart from one study which recruited institutionalized adults and was conducted in Taiwan. Baseline blood pressure readings were in the hypertensive range in eight of the studies in which both systolic and diastolic readings were

Fig. 1



Trial selection flow diagram. BP, blood pressure; RCT, randomized controlled trial.

reported. Three studies were in normotensive individuals, and, of these, one study reported MAP. Duration of intervention varied between 5 weeks and 12 months.

Study quality

The quality of the study design and reporting was variable. All studies reported random allocation, but there was insufficient detail given to ascertain adequate allocation concealment in most of them. Most studies mentioned withdrawals but only eight out of 11 studies gave reasons for withdrawal along with numbers of dropouts. One out of 11 trials clearly adhered to an intention-to-treat analysis whereas there was insufficient information to confirm this in most others. Groups were well balanced in seven out of 11 studies; nine out of 11 studies mentioned blinding with five studies describing blinding procedures. For the eight studies with a mean baseline blood pressure in the hypertensive range, a funnel plot of differences in systolic blood pressure between intervention and placebo groups did not suggest publication bias (Fig. 2).

Systolic blood pressure in studies with elevated mean baseline BP

Ten studies reported systolic blood pressure at baseline and follow-up. Four out of 10 studies reported the mean and standard deviation of change between baseline and follow-up for both groups. In the remaining studies, the standard deviation of change was imputed from the baseline and follow-up standard deviations. In eight studies, mean baseline systolic blood pressure was more than 140 mmHg. Data from these eight studies ($n = 545$) were combined using meta-analysis, which found a small, nonsignificant reduction in systolic blood pressure (−3.6 mmHg, 95% CI −8.0 to 0.7, $P = 0.1$) with significant heterogeneity between studies ($I^2 = 57\%$, $P = 0.02$). Details are given in Fig. 3.

Table 1 Study characteristics

Study	*N*	Latitude	Study population	Outcomes	Mean age	Sex (male%)	Intervention		Duration of intervention
							Control	Intervention	
Lind *et al.* [15], Sweden, 1987	29	59.8°N	Healthy volunteers with intermittent hypercalcaemia	Blood pressure	63	40	Placebo	Alphacalcidiol	6 months
Lind *et al.* [16], Sweden, 1988a	33	61°N	Patients with primary hyperparathyroidism	Blood pressure	65	19	Placebo	Alphacalcidiol	6 months
Lind *et al.* [17], Sweden, 1988b	65	59.8°N	Patients with impaired glucose tolerance	Blood pressure and glucose tolerance	Not stated	100	Placebo	Alphacalcidiol	12 weeks
Lind *et al.* [18], Sweden, 1989	42	61°N	Patients with mild-to-moderate hypertension	Blood pressure and plasma renin activity	51	80	Placebo	Alphacalcidiol	18 weeks
Myrup *et al.* [19], Denmark, 1992	74	55.6°N	Elderly female patients	Blood pressure, cholesterol, weight	70	0	Placebo	Cholecalciferol	12 months
Pan *et al.* [20], Taiwan, 1993	58	25°N	Institutionalized adults	Blood Pressure	74	78	Placebo	Cholecalciferol	11 weeks
Scragg *et al.* 21], England, 1995	95	52.2°N	Elderly patients	Blood pressure, cholesterol	70	54	Placebo	Cholecalciferol	5 weeks
Krause *et al.* [22], Germany, 1998	18	52.5°N	Mild hypertensive patients	Blood pressure	48	56	UVA	UVA + UVB	6 weeks
Pfeifer *et al.* [23], Germany, 2001	145	52°N	Elderly female patients	Blood pressure, cholesterol	75	0	Ca^{++} placebo	Ca^{++} Cholecalciferol	8 weeks
Schleithoff *et al.* [5], Germany, 2006	123	51.1°N	Heart failure patients	Blood pressure, cytokine levels, survival	55	83	Ca^{++} placebo	Ca^{++} Cholecalciferol	9 months
Sugden *et al.* [4], Scotland, 2008	34	56°N	Type 2 diabetes patients	Endothelial function, blood pressure, insulin sensitivity	64	53	Placebo	Ergocalciferol	8 weeks

UVA, ultraviolet A; UVB, ultraviolet B.

Table 2 Blood pressure reduction by study

Study	Baseline BP (mmHg)	Baseline 25OHD level	Daily dose equivalent	Difference in SBP reduction (mmHg)	Difference in DBP reduction (mmHg)
Hypertensive at baseline (mean systolic BP > 140 mmHg)					
Lind *et al.* [15], 1987	151/87	ND	1 μg 1,25 D	−4	−9.2
Lind *et al.* [16], 1988a	149/88	ND	1 μg 1,25 D	+3	−6.7
Lind *et al.* [17], 1988b	149/87	ND	0.75 μg 1,25 D	−4	−1.6
Lind *et al.* [18], 1989	157/99	ND	1 μg 1,25 D	+5	+0.4
Scragg *et al.* [21], 1995	148/82	33 nmol/l	2900 IU D3	0	0
Krause *et al.* [22], 1998	148/92	48 nmol/l	UVB light	−6	−8
Pfeifer *et al.* [23], 2001	142/84	25 nmol/l	800 IU D3	−6.5	−0.3
Sugden *et al.* [4], 2008	141/81	38 nmol/l	1800 IU D2	−13.9	−5.5
Normotensive at baseline (mean systolic BP ≤ 140 mmHg or MAP < 105 mmHg)					
Myrup *et al.* [19], 1992	MAP 102	ND	0.5 μg 1,25 D	MAP +1	–
Pan *et al.* [20], 1993	135/76	63 nmol/l	200 IU D3	−0.2	+1.3
Schleithoff *et al.* [5], 2006	123/75	37 nmol/l	2000 IU D3	+1	−1

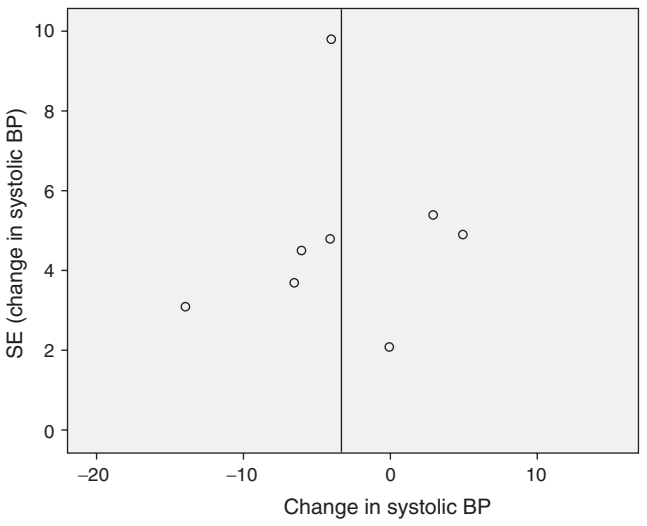
25OHD, 25 hydroxyvitamin D; DBP, diastolic blood pressure; MAP, mean arterial pressure; ND, no data available; SBP, systolic blood pressure; UVB, ultraviolet B.

For diastolic blood pressure, the mean change was −3.1 mmHg (95% CI −5.5 to −0.6, $P = 0.01$) for the intervention group compared with the placebo group. There was again significant heterogeneity between studies ($I^2 = 62\%$, $P = 0.01$). Details are given in Fig. 4.

Blood pressure changes in studies with normal mean baseline BP

Three reports concerned the effect of supplementation on blood pressure in studies with a mean baseline blood pressure that was not elevated. Two studies reported both systolic as well as diastolic blood pressure whereas the other reported MAP. These studies were therefore not combined in a meta-analysis. None of these studies showed a significant effect on blood pressure (Table 2).

Fig. 2



Funnel plot of outcome vs. study size. BP, blood pressure; SE, standard error.

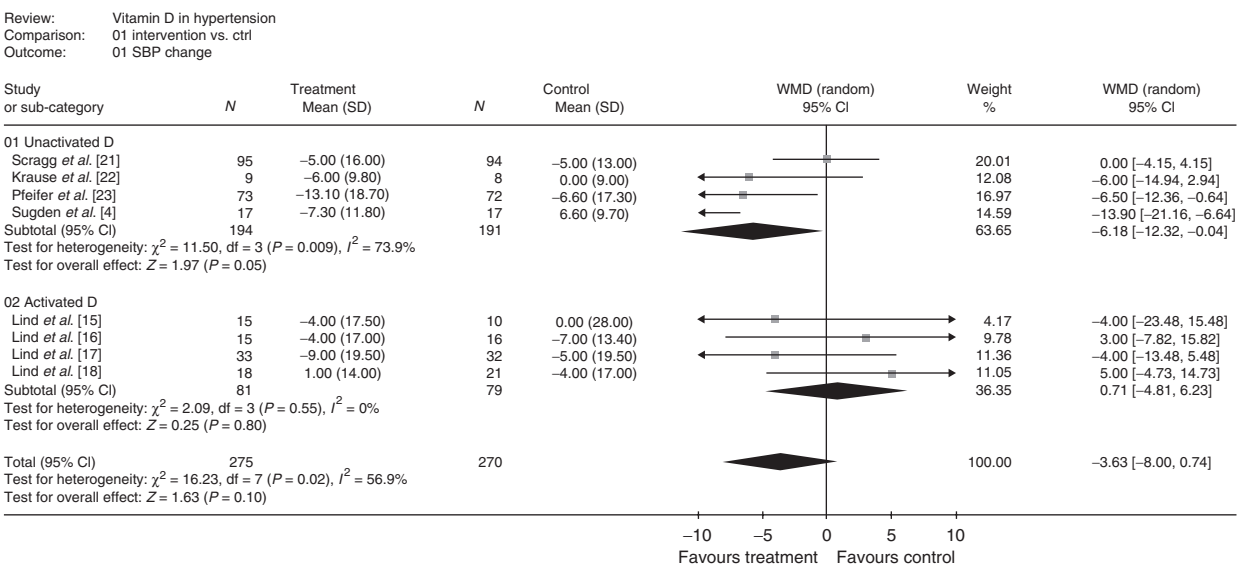
Activated vs. unactivated forms of vitamin D

In a subgroup analysis (Figs 3 and 4), we compared the effect of use of unactivated forms of vitamin D (vitamin D2, D3 and UVB radiation) vs. activated forms (calcitriol/1-alpha calcidiol) on change in blood pressure. The overall change in systolic BP was −6.2 mmHg (95% CI −12.32 to −0.04, $P = 0.05$) in the unactivated subgroup. In contrast, there was no significant decrease (+0.7 mmHg, 95% CI −4.8 to 6.2, $P = 0.8$) in systolic BP in which activated forms of vitamin D were used. These differences were not present in relation to changes in diastolic BP with a change of −2.6 mmHg (95% CI −5.8 to 0.7, $P = 0.13$) in the unactivated subgroup compared with −3.8 mmHg (95% CI −8.0 to 0.4, $P = 0.08$) in the activated subgroup. Significant heterogeneity remained after dividing studies into the above subgroups. Although the most likely mechanism of UVB light is via vitamin D production, it is possible that other mechanisms could be responsible for the antihypertensive effect seen in the study by Krause *et al.* [22]. Meta-analysis of the other seven studies, omitting this study, gave a change in systolic BP of −3.3 mmHg (95% CI −8.2 to 1.7, $P = 0.19$) and a change in diastolic BP of −2.3 (95% CI −4.6 to 0.0, $P = 0.05$).

Effects on other cardiovascular risk factors

Few studies included information about the effect of vitamin D on other cardiovascular risk factors. One study in patients with type 2 diabetes showed a significant improvement in endothelial function as measured by flow-mediated dilatation of the brachial artery [4]. No significant change was seen in insulin-mediated glucose uptake in those with impaired glucose tolerance [17]. No significant improvement was seen in glycated haemoglobin levels in patients with type 2 diabetes [4]. No significant effects on serum lipids were seen in a total of five studies [21,23,24]; in one study of postmenopausal women, an increase in total cholesterol was noted in the vitamin D treatment arm [19]. For patients with chronic heart failure, no difference was seen in survival over a

Fig. 3



Meta-analysis of effects of vitamin D on systolic blood pressure in studies with patients with mean baseline systolic BP > 140 mmHg. BP, blood pressure; CI, confidence interval; df, degrees of freedom; SBP, systolic blood pressure.

15-month period [5]. No deaths were reported in one other study with a follow-up of 5 weeks [21]. Survival data were not reported in the other studies.

Discussion

Key findings

Our meta-analysis has shown a small but significant fall in diastolic blood pressure but no significant fall in systolic blood pressure with vitamin D supplementation in studies in which the mean blood pressure was elevated at baseline. Systolic blood pressure reduction was more pronounced in those who received unactivated forms of vitamin D as compared with those who were given activated forms. The results of blood pressure reduction showed significant heterogeneity, and it was not possible to discern the source of heterogeneity with confidence. No reduction in blood pressure was observed in those who had normal baseline blood pressure.

Strengths and weaknesses

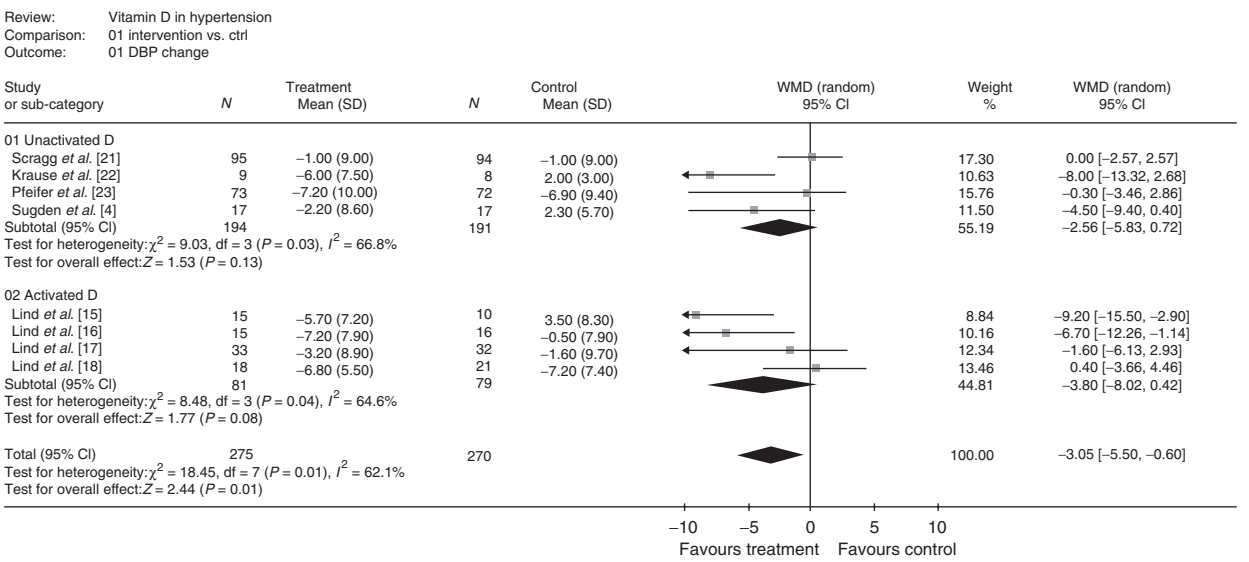
As with any systematic review, it is possible that some published or unpublished studies have eluded our search strategy. The strength of our findings is limited by the variable study quality, small number of studies, and significant heterogeneity of interventions, intervention duration, populations and outcomes. All included studies had small numbers of participants. Lack of appropriate statistical data in some reports necessitated imputation of standard deviations, which weakens the CIs calculated in the meta-analyses. For all of these reasons, the figures derived from the meta-analyses should be treated with considerable caution. It was not possible to examine the effect of baseline 25 hydroxyvitamin D status or dose on blood pressure reduction, as few studies reported baseline levels and dosing regimens were heterogenous. Furthermore, few studies described a rigorous methodology for measuring blood pressure, such as the use of random-zero sphygmomanometers, multiple readings or automated measurement. The quality of the blood pressure data may therefore have been suboptimal compared with current methods used in randomized controlled trials of antihypertensive interventions.

Study findings in context

Evidence from this systematic review provides weak evidence for a small reduction in blood pressure using vitamin D compounds in patients with hypertension but does not support any effect in those without hypertension. Although the blood pressure reductions reported here are modest at the level of the individual, a 3 mmHg fall in systolic blood pressure translates to approximately a 10% reduction in cardiovascular deaths at the population level [25]. If large population-level trials replicated this level of blood pressure reduction, a significant public health benefit could therefore accrue if vitamin D supplementation was undertaken for a large number of individuals with hypertension. However, the current evidence, though suggestive of an interesting effect, is certainly not robust enough to underpin use of vitamin D to reduce blood pressure in clinical practice.

Our findings accord with existing data that suggest that vitamin D supplementation may reduce overall mortality by approximately 7% in intervention studies

Fig. 4



Meta-analysis of effects of vitamin D on diastolic blood pressure in studies with patients with mean baseline systolic BP > 140 mmHg. BP, blood pressure; CI, confidence interval; df, degrees of freedom; DBP, diastolic blood pressure.

in osteoporosis [12]. This reduction is far higher than can be explained simply by a reduction in osteoporotic fractures, and it is therefore possible that reductions in cancer and cardiovascular deaths underlie this finding. Our findings also accord with the epidemiological data; interestingly, observational studies suggest a much stronger association between cardiovascular events and low vitamin D levels in patients with hypertension [8]. We found no effect of activated vitamin D analogues on systolic blood pressure in this meta-analysis. Although this may be a chance finding, it is of noteworthy that a recent meta-analysis of the effect of vitamin D in patients with renal failure (all of whom required activated vitamin D) found no effect on all-cause mortality [26]. Biological mechanisms that could explain this observation remain to be elucidated; though activated (1,25 hydroxyvitamin D) is assumed to underpin the biological effects of vitamin D therapy, it has become apparent that different vitamin D analogues have differential effects on calcium regulation compared with effects on cardiovascular systems, for example, control of renin levels [27]. Furthermore, 25 hydroxyvitamin D appears to have much more potent effects on the control of PTH production by parathyroid cells than 1,25 hydroxyvitamin D [28] – and PTH is itself known to exert deleterious effects on vascular function.

The large Women's Health Initiative study was not eligible for inclusion in our meta-analysis, as it compared calcium and a small dose of vitamin D with placebo. No effect on blood pressure was seen in this study [29], but this result does not rule out an effect of vitamin D on blood pressure; 80% of patients enrolled in this trial were normotensive at baseline, the dose (400 IU per day) of vitamin D3 used was very low, adherence to study medication was low at 60% and the increase in 25 hydroxyvitamin D levels seen in the intervention group was small [30].

Future work

The current evidence base for blood pressure reduction is based on a small number of studies of variable quality, many of which did not explicitly set out to study patients with hypertension. Further interventional studies are therefore needed to define the optimum dose, dosing interval and type of vitamin D to administer. This is a highly interesting scientific topic with potentially considerable public health relevance. Studies are required to confirm the magnitude of effect of vitamin D on blood pressure reduction, particularly in patients with hypertension, followed by large studies examining the effect of vitamin D on cardiovascular events and death.

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A.D.S. and M.D.W. are authors on one of the articles included in this systematic review.

There are no conflicts of interest.

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