Calcium supplementation for the management of primary hypertension in adults

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Abstract

Background
Metabolic studies suggest calcium may have a role in the regulation of blood pressure. Some epidemiological studies reported people with a higher intake of calcium tend to have lower blood pressure. Previous systematic reviews and meta-analyses reached conflicting conclusions about whether oral calcium supplementation can reduce blood pressure.

Objective
To evaluate the effects of oral calcium supplementation as a treatment for primary hypertension in adults.

Search strategy
We searched the Cochrane Library, MEDLINE, EMBASE, Science Citation Index, ISI Proceedings, ClinicalTrials.gov, Current Controlled Trials, CAB abstracts, and reference lists of systematic reviews, meta-analyses and randomised controlled trials (RCTs) included in the review.

Selection criteria
Inclusion criteria were: 1) RCTs comparing oral calcium supplementation with placebo, no treatment, or usual care; 2) treatment and follow-up ≥8 weeks; 3) participants over 18 years old, with raised systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥85 mmHg; 4) SBP and DBP reported at end of follow-up. We excluded trials where: participants were pregnant; received antihypertensive medication which changed during the study; or calcium supplementation was combined with other interventions.

Data collection and analysis
Two reviewers independently abstracted data and assessed trial quality. Disagreements were resolved by discussion or a third reviewer. Random effects meta-analyses and sensitivity analyses were conducted.

Main results
We included 13 RCTs (n=485), with between eight and 15 weeks follow-up. The results of the individual trials were heterogeneous. Combining all trials, participants receiving calcium supplementation as compared to control had a statistically significant reduction in SBP (mean difference: -2.5 mmHg, 95% CI: -4.5 to -0.6, I² = 42%), but not DBP (mean difference: -0.8 mmHg, 95% CI: -2.1 to 0.4, I² = 48%). Sub-group analyses indicated that heterogeneity between trials could not be explained by dose of calcium or baseline blood pressure. Heterogeneity was reduced when poor quality trials were excluded. The one trial reporting adequate concealment of allocation and the one trial reporting adequate blinding yielded results consistent with the primary meta-analysis.

Reviewers' conclusions
Due to poor quality of included trials and heterogeneity between trials, the evidence in favour of causal association between calcium supplementation and blood pressure reduction is weak and is probably due to bias. This is because poor quality studies generally tend to over-estimate the effects of treatment. Larger, longer duration and better quality double-blind placebo controlled trials are needed to assess the effect of calcium supplementation on blood pressure and cardiovascular outcomes.

Synopsis
This review did not find robust evidence that oral calcium supplementation reduces high blood pressure in adults. It reviewed 13 trials enrolling 485 people, which compared calcium supplementation with placebo or no treatment, and measured blood pressure 8 to 15 weeks later. On average, people receiving extra calcium achieved slightly lower systolic blood pressure at the end of trials. However, most trials were of poor quality, so their results may not be reliable. Trials were too small and short to measure whether extra calcium reduces the risk of death, heart attack or stroke. Calcium usually had no more adverse effects than placebo. Larger, longer duration, better quality trials are needed to clarify whether calcium supplementation can lower high blood pressure.

Background
High blood pressure (BP), or hypertension, is associated with a variety of structural changes in the blood vessels and heart which can lead to cardiovascular disease, stroke and renal diseases. It is one of the ten leading risk factors influencing the global burden of disease and is estimated to lead to over 7 million deaths each year, about 13% of the total deaths worldwide (WHO 2002). Reducing blood pressure levels is associated with significant reduction in cardiovascular and cerebrovascular morbidity and mortality (MacMahon 1990; PSC 2002). The most common form of hypertension, occurring in around 95% of all cases, is primary hypertension which is defined as high blood pressure with no identifiable cause (Brown 1997). Secondary hypertension is high blood pressure with an identifiable cause, e.g. renal disease or endocrine disturbances.

Epidemiological evidence about the effects of dietary calcium intake on blood pressure is unclear. Although some epidemiological studies, especially those in populations with low intakes of dietary calcium, report an inverse association between calcium intake and blood pressure, other studies report conflicting results (Hamet 1995; Cutler 1990; Burgess 1999; Cappuccio 1995). This could be because of different recruitment protocols and different methods of measuring blood pressure, assessing dietary calcium intake, and statistical analysis. Due to these inconsistencies and to the difficulties in drawing conclusions about single nutrients from survey data, it is not at present possible to make a definitive link between calcium intake and blood pressure.
Despite numerous clinical studies in humans, the mechanism whereby dietary calcium might affect blood pressure is unclear, although it is plausible that it may affect the concentrations of free intracellular calcium ions, which are known to regulate blood pressure (Hamet 1995; Newson 1986). It is also possible that the hypertensive effect of sodium chloride (common salt) may be affected by consumption of calcium, in particular that calcium may lower blood pressure in people with a low calcium but high sodium diet (Kotchen 1998).

While studies in animals have provided more consistent evidence of a link between dietary calcium and blood pressure, most studies were in young animals and demonstrated that calcium prevented the rise in blood pressure associated with aging (Hamet 1995). However, studies in animals may not be relevant to humans.

We found two reviews (Burgess 1999; Hamet 1995) and several meta-analyses (Bucher 1996; Cappuccio 1989; Cutler 1990; Griffith 1999; Allender 1996) summarising the findings of randomised controlled trials of oral calcium supplements on blood pressure in both normotensive and hypertensive participants. The 3 meta-analyses which carried out sub-group analyses of hypertensive participants reported different overall findings: no significant change in blood pressure (Cappuccio 1989), a significant reduction in SBP only (Allender 1996), and a significant reduction in both systolic and DBP (Bucher 1996). However, they all included studies which treated participants with calcium for only short periods e.g. less than 2 weeks. Furthermore, conflicting results may be due to the effect of calcium supplementation being influenced by dietary calcium intake, vitamin D status, type of medication (e.g. calcium antagonists), or degree of elevation of blood pressure.

The aim of this review was to summarise the evidence about the benefits and harms of dietary calcium supplementation for patients with primary hypertension, in order to inform decisions about recommendations for treatment.

Results

Discussion

Effect of intervention

Our meta-analysis of 13 randomised controlled trials enrolling 485 participants, with between eight and 15 weeks follow-up, found that calcium supplementation was associated with a statistically significant reduction in SBP (mean difference: -2.5, 95% CI: -4.5 to -0.6), but had little effect on DBP. Funnel plots showed little evidence of publication bias. As the majority of trials were not of good quality (see below), the results of the primary meta-analyses must be interpreted with caution.

There was substantial heterogeneity between the findings of the trials (I² = 42% and 48% for SBP and DBP respectively), which could reflect heterogeneity in either the patient populations, the interventions or the methods used in the trials. Some of these possible confounding factors were evaluated by sub-group analyses. Sub-group analyses by dose of calcium supplementation showed little difference in estimated treatment effect between trials administering higher and lower doses. Likewise, sub-group analyses showed little difference in response in relation to mean baseline blood pressure. Hence it seems unlikely that either dose of calcium or baseline blood pressure explain the heterogeneity. However, other differences between the populations studied, e.g. dietary calcium status, use of anti-hypertensive drugs, were not amenable to sub-group analysis. Furthermore, findings from multiple subgroup analyses may be misleading as subgroup analyses are observational by nature and not based on randomised comparisons (Cochrane Handbook; Juni 2001). False positive and false negative significance tests increase in likelihood as more subgroup analyses are performed. When we excluded trials which did not confirm binding of the participant and the treatment provider; heterogeneity between trials was reduced (I² = 17% and 39% for SBP and DBP respectively); when we excluded trials which did not report the standard deviation of the treatment effect, there was little heterogeneity between trials (I² = 0% and 19% for SBP and DBP respectively). These sensitivity analyses suggest that the poor quality trials are contributing to the heterogeneity.

The review of Takagi 1991 reported an unusually large reduction in blood pressure with calcium supplementation. This trial measured mean hourly BP averaged over 24 hours, whereas all other trials measured BP at one clinic visit. This could suggest a diurnal effect of calcium that was not detected by the other trials. However, this was a cross-over trial with only 9 subjects and thus requires confirmation by a larger trial.

Withdrawals were reported in 11 trials enrolling 374 participants; overall the rate of withdrawal was similar in treatment and control groups. As reasons for withdrawals were not well reported, we were not able to distinguish between withdrawals due to adverse effects and lack of persistence. However, discontinuation of treatment for any reason would need to be taken into account in framing recommendations. Adverse effects were reported by treatment arm in only 6 trials. The most commonly reported adverse effects were gastrointestinal symptoms and headache. These were reported at a similar frequency in the calcium and control groups.

As expected, participants receiving calcium supplements had higher serum calcium levels than those in the control groups. One trial reported a DBP reduction of 1.6 mmHg more in participants receiving calcium than those who did not receive calcium (Grobbee 1986); one trial reported no association between SBP and serum calcium levels (Kawano 1998). We were unable to investigate possible relationships between change in blood pressure and change in serum calcium levels through meta-regression, due to the small number of trials reporting serum calcium, without the risk of spurious false positive findings (Higgins 2003).

Discussion

Conclusion

This meta-analysis demonstrated a statistically significant reduction in systolic blood pressure and no reduction in diastolic blood pressure with calcium supplementation as compared to control. It also demonstrated evidence that calcium supplementation is not...
associated with adverse effects. However, in view of the poor quality of the trials and the heterogeneity between the trials, we conclude that the evidence in favour of a causal association between calcium supplementation and blood pressure reduction is weak. It is our opinion that, as poor quality studies generally tend to over-estimate the effects of treatment, the apparently significant reduction in systolic blood pressure is more likely to be due to bias. However, a decrease in systolic blood pressure with calcium supplementation cannot be discounted.

Even if increasing calcium intake results in a reduction in systolic blood pressure, this reduction is small, 2.5 mmHg, is not known to be sustained beyond 15 weeks and is not known to cause a decrease in morbidity and mortality. This is compared to the evidence for drugs, which singly result in an average reduction of about 9.1 mmHg (95% CI: 8.8 to 9.3) in SBP and 5.5 mmHg (95% CI: 5.4 to 5.7) in DBP (Law 2003), are known to have sustained effects and to reduce morbidity and mortality. However, even small changes in blood pressure in large proportions of the population in a common condition such as hypertension could reduce adverse cardiovascular outcomes. Hence, if a clear sustained effect of calcium supplementation on blood pressure were established, an increase in dietary calcium at a population level could have important benefits.

**Reviewers' conclusions**

**Implications for practice**

Overall we did not find robust enough evidence that dietary calcium supplementation reduced raised blood pressure to justify its use as a treatment for elevated blood pressure.

**Implications for research**

More placebo controlled trials are warranted to clarify whether calcium supplementation can reduce blood pressure in people with elevated blood pressure. These trials should be randomized, with adequate concealment of allocation of participants to treatment arms, double-blinded and large enough and of at least one year duration in order to be able to detect a sustained effect of calcium supplementation on blood pressure. Large longer term placebo controlled trials of calcium for other indications (eg. osteoporosis) should also report blood pressure and cardiovascular outcomes.

**References to studies included in this review**


Grobbee 1986 *(published data only)*


Lyle 1992 *(published data only)*


Martinez 1985 *(published data only)*


McCarron 1985 *(published data only)*


Morris 1988 *(published data only)*

Morris CD, Karanja N, McCarron DA. Dietary versus supplemental calcium to reduce blood pressure. Clinical Research 1988;36:A139-.

Nowson 1989 *(published data only)*


Sanchez 1997 *(published data only)*


Strazzullo 1986 *(published data only)*


Takagi 1991 *(published data only)*


Tanjri 1991 *(published data only)*


Weinberger 1993 *(published data only)*


Zoccali 1988 *(published data only)*


* indicates the major publication for the study

**References to studies excluded from this review**

Appel 1995 *(published data only)*


Belizan 1991 *(published data only)*


Buonopane 1992 *(published data only)*

Cappuccio 1987(a) \{published data only\}

Cappuccio 1987(b) \{published data only\}

Davis 1996 \{published data only\}

Feinleib 1984 \{published data only\}

Gruchow 1988 \{published data only\}

Hebert 1995 \{published data only\}

Hollis 1995 \{published data only\}

Jespersen 1993 \{published data only\}

Johnson 1985 \{published data only\}

Kromhout 1985 \{published data only\}

Kynast-Gales 1992 \{published data only\}

Lyle 1987 \{published data only\}

Lyle 1988 \{published data only\}

MacGregor 1987 \{published data only\}

Meese 1987 \{published data only\}

Morris 1992 \{published data only\}

Pan 1993 \{published data only\}

Petersen 1994 \{published data only\}

Sacks 1994 \{published data only\}

Schneider 1995 \{published data only\}

Siamani 1988 \{published data only\}

Siania 1988 \{published data only\}

Thomsen 1987 \{published data only\}

TOHP 1992 \{published data only\}
The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. JAMA 1992;267:1213-1220.

van Berestein 1986 \{published data only\}

Vinson 1987 \{published data only\}

Yamamoto 1995 \{published data only\}
Zemel 2005 (published data only)

Zhou 1994 (published data only)

Zoccali 1987 (published data only)

Additional references
Allender 1996

Australian 1989

BNF 2004
British National Formulary 47. 2004:-.

Brown 1997

Bruck 1999

Bucher 1996

Burgess 1999

Cappuccio 1989

Cappuccio 1995

Cochrane Handbook

Curtin 2002

Cutter 1990

DASH 1999

DASH 2000

DerSimonian 1986

Dickersin 1994

Egger 2003
Egger M, Juni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. 2003:-.


Elbourne 2002

Egger 1999

Hamet 1995

Higgins 2002

Higgins 2003

JNC VII 2003

June 2001

Kawano 1998 (B)

Kochten 1998

Law 2003

MacMahon 1990
Moher 1998
Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. Lancet 1998;352:609-613.

NIH 2000

Nowson 1986

PSC 2002

Schulz 1995

Sunderrajan 1984

WHO 2002

Graphs

Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

### Calcium vs control (parallel trials only)

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>5</td>
<td>250</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-3.22 [-6.19, -0.24]</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>5</td>
<td>250</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-2.39 [-4.79, 0.01]</td>
</tr>
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</table>

### Calcium vs control (crossover trials only)

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>8</td>
<td>428</td>
<td>MD in SBP (Random, 95% CI)</td>
<td>-2.30 [-4.88, 0.28]</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>8</td>
<td>428</td>
<td>MD in DBP (Random, 95% CI)</td>
<td>-0.28 [-1.66, 1.10]</td>
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### Calcium vs control (calcium dose subgroups)

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>13</td>
<td></td>
<td>MD in SBP (Random, 95% CI)</td>
<td>-2.53 [-4.45, -0.60]</td>
</tr>
<tr>
<td>1.1 Calcium dose 1.2-2g/day</td>
<td>5</td>
<td></td>
<td>MD in SBP (Random, 95% CI)</td>
<td>-2.69 [-5.86, 0.47]</td>
</tr>
<tr>
<td>1.2 Calcium dose &lt;1.2g/day</td>
<td>8</td>
<td></td>
<td>MD in SBP (Random, 95% CI)</td>
<td>-2.67 [-5.15, -0.18]</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>13</td>
<td></td>
<td>MD in DBP (Random, 95% CI)</td>
<td>-0.81 [-2.07, 0.44]</td>
</tr>
<tr>
<td>2.1 Calcium dose 1.2-2g/day</td>
<td>5</td>
<td></td>
<td>MD in DBP (Random, 95% CI)</td>
<td>-0.78 [-3.82, 2.25]</td>
</tr>
<tr>
<td>2.2 Calcium dose &lt;1.2g/day</td>
<td>8</td>
<td></td>
<td>MD in DBP (Random, 95% CI)</td>
<td>-0.75 [-2.13, 0.63]</td>
</tr>
</tbody>
</table>

### Calcium vs control (baseline BP subgroups)

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
</table>
1 Systolic blood pressure 13 MD in SBP (Random, 95% CI) -2.53 [-4.45, -0.60]
1.1 Higher baseline blood pressure (SBP>145 mmHg) 7 MD in SBP (Random, 95% CI) -2.49 [-4.11, -0.86]
1.2 Lower baseline blood pressure (SBP<=145 mmHg) 6 MD in SBP (Random, 95% CI) -3.33 [-7.37, 0.72]
2 Diastolic blood pressure 13 MD in DBP (Random, 95% CI) -0.81 [-2.07, 0.44]
2.1 Higher baseline blood pressure (SBP>145 mmHg) 7 MD in DBP (Random, 95% CI) -0.38 [-1.35, 0.58]
2.2 Lower baseline blood pressure (SBP<=145 mmHg) 6 MD in DBP (Random, 95% CI) -2.16 [-4.76, 0.45]

Calcium vs control: excluding trials not confirming double blinding

<table>
<thead>
<tr>
<th>Outcome title</th>
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<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Systolic BP</td>
<td>10</td>
<td>473</td>
<td>MD in SBP (Random, 95% CI)</td>
<td>-1.93 [-3.81, -0.06]</td>
</tr>
<tr>
<td>2 Diastolic BP</td>
<td>10</td>
<td>514</td>
<td>MD in DBP (Random, 95% CI)</td>
<td>-0.34 [-1.72, 1.03]</td>
</tr>
</tbody>
</table>

Calcium vs control: excluding trials not reporting SD

<table>
<thead>
<tr>
<th>Outcome title</th>
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<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Systolic BP</td>
<td>7</td>
<td></td>
<td>MD in SBP (Random, 95% CI)</td>
<td>-2.75 [-4.28, -1.23]</td>
</tr>
<tr>
<td>2 Diastolic BP</td>
<td>7</td>
<td></td>
<td>MD in DBP (Random, 95% CI)</td>
<td>-1.44 [-2.74, -0.14]</td>
</tr>
</tbody>
</table>

Calcium vs control: (parallel trials)

<table>
<thead>
<tr>
<th>Outcome title</th>
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<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Withdrawal from treatment (all causes)</td>
<td>3</td>
<td>161</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.00 [-0.06, 0.06]</td>
</tr>
</tbody>
</table>

Calcium vs control: (parallel trials)

<table>
<thead>
<tr>
<th>Outcome title</th>
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<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Diarrhoea</td>
<td>2</td>
<td>161</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.02 [-0.09, 0.05]</td>
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Calcium vs control: (crossover trials)

<table>
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<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Gastro-intestinal effects (including diarrhoea)</td>
<td>3</td>
<td>178</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.01 [-0.09, 0.08]</td>
</tr>
</tbody>
</table>

Calcium vs control

<table>
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<tr>
<th>Outcome title</th>
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<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Serum calcium</td>
<td>8</td>
<td>487</td>
<td>MD in serum Ca (Random, 95% CI)</td>
<td>0.04 [0.02, 0.06]</td>
</tr>
</tbody>
</table>