6. Recommendations on potassium, magnesium and calcium

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Abstract

Objective: To provide updated, evidence-based recommendations on the consumption, through diet, and supplementation of the cations potassium, magnesium and calcium for the prevention and treatment of hypertension in otherwise healthy adults (except pregnant women).

Options: Dietary supplementation with cations has been suggested as an alternative or adjunctive therapy to antihypertensive medications. Other options include other nonpharmacologic treatments for hypertension.

Outcomes: The health outcomes considered were changes in blood pressure and in morbidity and mortality rates. Because of insufficient evidence, no economic outcomes were considered.

Evidence: A MEDLINE search was conducted for the period 1966–1996 with the terms hypertension and potassium, magnesium and calcium. Reports of trials, meta-analyses and review articles were obtained. Other relevant evidence was obtained from the reference lists of articles identified, from the personal files of the authors and through contacts with experts. The articles were reviewed, classified according to study design, and graded according to the level of evidence.

Values: A high value was placed on the avoidance of cardiovascular morbidity and premature death caused by untreated hypertension.

Benefits, harms and costs: The weight of the evidence from randomized controlled trials indicates that increasing intake of or supplementing the diet with potassium, magnesium or calcium is not associated with prevention of hypertension, nor is it effective in reducing high blood pressure. Potassium supplementation may be effective in reducing blood pressure in patients with hypokalemia during diuretic therapy.

Recommendations: For the prevention of hypertension, the following recommendations are made: (1) The daily dietary intake of potassium should be 60 mmol or more, because this level of intake has been associated with a reduced risk of stroke-related mortality. (2) For normotensive people obtaining on average 60 mmol of potassium daily through dietary intake, potassium supplementation is not recommended as a means of preventing an increase in blood pressure. (3) For normotensive people, magnesium supplementation is not recommended as a means of preventing an increase in blood pressure. (4) For normotensive people, calcium supplementation above the recommended daily intake is not recommended as a means of preventing an increase in blood pressure. For the treatment of hypertension, the following recommendations are made: (5) Potassium supplementation above the recommended daily dietary intake of 60 mmol is not recommended as a treatment for hypertension. (6) Magnesium supplementation is not recommended as a treatment for hypertension. (7) Calcium supplementation above the recommended daily dietary intake is not recommended as a treatment for hypertension.

Validation: These guidelines are consistent with the results of meta-analyses and recommendations made by other organizations. They have not been clinically tested.

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In 1931 recommendations for hypertensive patients regarding dietary intake of and supplementation with potassium, calcium and sodium were published in *CMAJ*.[1] Since then, the methodology for conducting and reporting clinical and other research, for reviewing the literature and for formulating recommendations has changed considerably. Over the years, there has been a belief that a diet high in sodium or low in potassium, magnesium or calcium predisposes people to high blood pressure and that correcting such diets would bring blood pressure to normal levels. An extreme diet of rice and fruit has been used as an in-hospital or urgent treatment for hypertension because it makes these dietary corrections. Although

Special supplement

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such a diet reduces both blood pressure and body weight, it is not practical as a long-term therapy. However, patients were often counselled to make these dietary adjustments.

The primary objective of this guideline is to review contemporary clinical research on the relation between 3 cations (potassium, magnesium and calcium) and blood pressure and to advise health care professionals and the public accordingly about the prevention and treatment of hypertension in otherwise healthy adults (except pregnant women) in the ambulatory care setting.

Methods

A complete description of the methods used in developing these recommendations is given in part 1 of this supplement.[2]

The chair and members of the panel were selected by the Organizing Committee for the lifestyle modification recommendations to obtain a spectrum of health care professionals and scientists with expertise and interest in the dietary aspects of hypertension prevention and control.

A MEDLINE search of the English and French literature was performed for the period 1966–1996 with the term hypertension and the terms potassium, magnesium and calcium used in sequential searches. Secondary searches were done using the references found in review articles and meta-analyses. Additional articles were identified by reviewing the reference lists of the identified articles, were found in the personal files of the panel members and were suggested by other experts. The principles for grading the evidence and the recommendations were based on those previously used by the Canadian Hypertension Society[3] and are summarized in part 1 of this supplement.[2]

An attempt was made to reach consensus on all recommendations. The evidence and the recommendations were presented for comment to the other expert panels for this guidelines series, submitted for review to major Canadian organizations and presented at an international conference on preventive cardiology, to allow further national and international input. All revisions were reviewed and assessed by the panel before incorporation into the final document.

Results

Potassium supplementation

Epidemiologic studies relating dietary intake of potassium and blood pressure were reviewed to provide a basis for understanding the intervention studies, even though such epidemiologic studies should not influence the drafting of recommendations. In those studies, dietary intake of potassium was estimated using different methods, including dietary recall or diet records, food frequency questionnaires and urine collection. Urine collection was done as 24-hour collections, overnight collections or spot collections; the results were expressed as total potassium content or as a ratio of total potassium content to urine creatinine content or urine sodium content.

Khaw and Barrett-Connor[4] reported the results of a 12-year prospective cohort from the Rancho Bernardo project and demonstrated that the relative risk of stroke-associated death in the lowest tertile of potassium intake, compared with the top 2 tertiles combined, was 2.6 (difference not significant) for men and 4.8 ($p = 0.01$) for women. A 10-mmol increase in daily potassium intake was associated with a 40% reduction in risk of death from stroke ($p < 0.001$). This effect was apparently independent of other dietary variables and known cardiovascular risk factors. Some cross-sectional studies of other populations, including normotensive and hypertensive people, have demonstrated an association between estimated dietary potassium intake and blood pressure,[5–13] although other studies have not[14–21] (Table 1). Although the results of some epidemiologic studies are consistent with a link between diets high in potassium and the prevention of hypertension or hypertension-associated death, or both, these data cannot form the basis of recommendations when the results of intervention trials are available.

In evaluating intervention studies of potassium supplementation, we found no trials that examined the effect of supplementation on morbidity and mortality rates. There have been several level II intervention trials assessing the effect of increased potassium intake on blood pressure in hypertensive subjects; most of these used supplements rather than increasing dietary intake. In the pre-eminent trial of potassium supplementation, Grimm and associates[22] conducted a randomized controlled trial in which 287 hypertensive men were randomly assigned to receive 96 mmol of potassium chloride per day or placebo for 2.2 years. Because antihypertensive medication had to be reinstated (the primary outcome variable) for 79 men in each group, long-term potassium supplementation appeared to be ineffective for treating hypertension. Other large trials[23–25] have shown no reduction in blood pressure, even with doses as high as 96 mmol of potassium chloride per day; the results of smaller trials have been mixed[26–45] (Table 2). Therefore, it appears that potassium supplementation is not effective in reducing blood pressure.

Studies with more than one change in diet or supplementation have been attempted; the design of such studies makes it difficult, if not impossible, to assess the role of potassium supplementation. Chalmers and colleagues[46] conducted a trial in which 212 untreated hypertensive patients were randomly assigned to 1 of 4 diet interventions: a control diet, a high-potassium diet (urinary potassium excretion of 97 mmol/day and urinary sodium excretion similar to that of subjects on the control diet), a low-sodium diet (urinary sodium excretion 86 mmol/day) and a low-sodium/high-potassium diet (urinary sodium excretion approximately 73 mmol/day and urinary potassium excretion 87 mmol/day). The reduction in blood pressure with either the low-sodium diet or the high-potassium diet was significant relative to the control diet. However, the combination diet did not result in any greater reduction in blood pressure than a single dietary change. Another study, conducted over 6 months, used potassium supplementation in combination with calcium or magnesium supplementation.[47] There was no statistically

significant effect of either treatment relative to placebo. In a separate trial of 100 patients with mild to moderate hypertension,[48] multiple changes in mineral intake (obtained by administering a low-sodium, high-potassium and high-magnesium salt substitute) were made over 24 weeks and resulted in only a modest reduction in systolic blood pressure. In the short-term DASH (Dietary Approaches to Stop Hypertension) trial[49] participants were randomly assigned for 6 months to a standard diet, a diet enhanced with fruits and vegetables, or a diet enhanced with fruits, vegetables and low-fat dairy products. Overall, for normotensive and hypertensive participants, the only significant reduction was in systolic blood pressure (level II evidence). For the 133 hypertensive subjects, the fruit-and-vegetable diet led to a change of –7.2/–2.8 mm Hg more than the control diet, and the combination diet led to a change of –11.4/–5.5 mm Hg more than the control diet (level III evidence). In the normotensive subjects, only the combination diet reduced blood pressure more than the control diet (level III evidence). Because of the multiple dietary changes, the confounding changes in other nutrients as the diets were changed and the inclusion of both normotensive and hypertensive subjects, it is difficult to understand the results of this short-term study.

There may be some distinct patient populations for whom potassium supplementation is useful, such as patients with diuretic-induced hypokalemia and patients of African descent. In a study by Kaplan and collaborators,[33] patients with hypokalemia from treatment with diuretic drugs experienced significant reductions in blood pressure when given 60 mmol of potassium daily for 6 weeks. However, in a substudy of the large hypertension studies conducted by the Medical Research Council in the United Kingdom,[23] patients randomly assigned to receive diuretic therapy underwent a secondary randomization to compare two diuretics and to assess the utility of potassium supplementation. In this setting, the use of potassium supplements over 3 years was not associated with any additional reduction of blood pressure.

There has been much discussion in the literature suggesting that black hypertensive patients may benefit from potassium supplementation. Obel[28] reported significant reductions in blood pressure (–39/–17 mm Hg) in a placebo-controlled study conducted in Africa in which 48 patients were ran-

Table 1: Epidemiology studies of the relation between dietary potassium (K) and blood pressure or hypertension

Method of assessing dietary K	Subjects	Results	Comments
Diet recall with dietitian[4]	859 men and women	10 mmol increase in dietary K associated with a stroke mortality RR of 0.56–0.65	12-yr prospective study; BP measured
Overnight urine K/Cr ratio[5]	574 normotensive and hypertensive	$r = –0.23$, $p < 0.001$	BP measured
24-hr urine collection[6]	662	Urinary K NS Urinary K/Na, $r = 0.163$, $p < 0.05$	Followed 3–4 yr; BP measured
Duplicate diet, 24-hr urine collection[7]	Blacks: 148 men, 208 women Whites: 342 men, 328	NS when other variables controlled	BP measured
Total body content, exchangeable serum K level[8]	91 hypertensive, 121 normotensive	Serum K, total body K, exchangeable K related to SBP and DBP	Diet was not assessed, patients drug-free; BP measured
Urine K/Cr ratio [9]	98 vegetarian, 98 nonvegetarian	Urinary K > 80 had lower BP	2% of vegetarians and 26% of nonvegetarians had hypertension; BP measured
Diet recall with dietitian[10]	309 men, 376 women	Diet K related to SBP	SBP was age-adjusted; BP measured
Overnight urine Na/K ratio[11]	1 939	Urinary Na/K related to DBP, $r = 0.15$, $p < 0.05$	Recruited in stroke cities; BP measured
Morning spot urine for K and Cr[12]	1 120	Urinary K/Cr related to SBP, $r = –0.10$, $p < 0.05$	Traditional Japanese lifestyle; BP measured
Diet recall[13]	11 667	Urinary Na/K and BP higher in blacks	NHANES-1 subset with no hypertension; BP measured
Diet recall[14]	8 000	Inconclusive	Intercorrelation between cations prevented assessment individually; BP measured
24-hr urine collection[15]	3 754 men, 3 600 women	$r = –0.04$ to 0.06	Very weak correlations; BP measured
24-hr urine collection[16]	10 079	Dietary K related to BP (pooled adjusted), $r = –0.0446$	In only 3 centres; BP measured
Diet recall with dietitian[17]	584 men, 718 women	Dietary Na/K ratio related to SBP and DBP	In both men and women; BP measured
FFQ[18]	58 218 women	No significant relation	4-yr follow-up; BP self-reported
FFQ[19]	30 681 men	No significant relation	BP self-reported
24-hr urine collection[20]	201 men	Urinary K/Cr related to SBP, $r = – 0.294$	BP measured
FFQ[21]	41 541 women	No significant relation	BP self-reported

Note: RR = relative risk, Cr = creatinine, Na = sodium, NS = nonsignificant, BP= blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, NHANES = National Health and Nutrition Examination Surveys database, FFQ = food frequency questionnaire.

domly assigned to receive 64 mmol of potassium daily for 16 weeks. Brancati and coworkers[50] conducted a study of black Americans with normal blood pressure, who were given a potassium-poor diet for 3 weeks and then randomly assigned to receive 80 mmol of potassium (as a supplement) or placebo for 3 weeks. In this contrived setting, potassium supplementation was associated with a reduction in blood pressure, but it is unclear how this study relates to clinical practice and hence it has not been included in our analysis of the evidence. Supporting studies are required before specific recommendations can be made for this distinct population.

Two meta-analyses[51,52] both suggested a small beneficial effect that may be related to the dietary intake of sodium. The more recent meta-analysis,[52] which covered treatment studies of potassium supplementation, suggested that supplementation be considered for patients with high sodium intake but stopped short of recommending supplementation for prevention and treatment of hypertension in everyone. This meta-analysis did not include the level II study by Grimm and associates[22] on the basis that sodium restriction was part of the intervention in that trial; however, 3 other studies that used combined sodium restriction and

Table 2: Treatment studies of potassium supplementation in hypertensive subjects

Study design	Subjects	Daily K dose, mmol	Duration	Dietary changes, mmol		Change in BP, mm Hg*	Comments
				Na	K		
Level II							
Double-blind placebo-controlled RCT[22]	287 men	96	2.2 yr	–18/8 h	+24/8 h	Not given	79 men per group restarted drugs
Double-blind placebo-controlled RCT[23]	1185	16.8–33.6	35 mo			No significant reduction	Dose of K low; diuretic treatment
Double-blind placebo-controlled RCT[24]	258 of 787	Diet 103	6 mo	–35	+13	–8.66/–7.91 NS	Subgroup of TAIM
Double-blind placebo-controlled RCT[25]	298	64	12 wk	+1	+39	–0.2/+0.6 NS	
Single blind[26]	47	> 30	1 yr		+45% (25 mmol)	NS	Inadequate power
Double-blind placebo-controlled RCT[27]	37	60	32 wk	–12	+20	–12.1/–13.1	
Double-blind placebo-controlled RCT[28]	48	64	112 d		+40	–39/–17	Conducted in Africa
Double-blind placebo-controlled RCT[29]	37	48	105 d	–6	+30	–14/–10.5	
Double-blind placebo-controlled RCT[30]	101	120	8 wk			–0.9/–1.3 NS	
Single-blind crossover[31]	32	65	6 wk	+35	+62	–7/–3 NS	
Double-blind crossover[32]	40	72	6 wk	+12	+57	–2.5/–0.6 NS	
Double-blind crossover[33]	16	60	6 wk	+1	+46	–5.6/–5.8	Diuretic-induced hypokalemia
Double-blind crossover[34]	12	140	2–6 wk	+5	+123	–1.9/–1.0 NS	
Double-blind crossover[35]	20	64	4 wk	+7	+50	–2.0/0 NS	
Double-blind crossover[36]	23	60	4 wk	+29	+56	–7.0/– 4.0	
Double-blind placebo-controlled RCT[37]	24	64	4 wk		+68	–6.3/–3.0	
Double-blind placebo-controlled RCT[38]	18	60	4 wk	+13	+39	–10/– 6	Elderly subjects
Double-blind crossover[39]	20	64	2 wk	+9	+52	–1.1/–2.5	Significant for DBP only
Double-blind crossover[40]	19	100	2 wk	+13	+81	–1.0/–3.0 NS	
Placebo-controlled, double-blind crossover[41]	12	120	8 d	–13	+104.9	NS	
Double-blind, randomized[42]	22	70	4 d	–29	+109	–8.6/–4.0	
Level IV							
Open crossover[43]	20	100	10 d	+25	+82	–11.1/–5.2	
Open, single-blind[44]	16	100	8 wk	+6	+87	–17/–10 NS	
Level V							
Open, single-blind[45]	10	96	12 d	–6	+63	–9/–2 NS	
Combination therapies							
Level II							
RCT[46]	212	Diet > 100	12 wk		+22	–3.9/–3.1	No additional reduction with low Na diet
Double-blind placebo-controlled RCT[47]	95	60	6 mo			NS	Combined with Mg and/or Ca supplements
Double-blind placebo-controlled RCT[48]	100	Ad lib use of salt substitute with K and Mg	6 mo	–32	+22	–7.6/–3.3	Significant for SBP only
RCT[49]	459	Diet	8 wk	–9	+32	–2.8/–0.3	Significant for SBP only

Note: RCT = randomized controlled trial, TAIM = Trial of Antihypertensive Interventions and Management.
*Statistically significant unless otherwise specified.

potassium supplementation were included in the meta-analysis, including that of Chalmers and colleagues,[46] which demonstrated that a combination of low sodium and high potassium did not reduce blood pressure any more than either intervention alone. The analysis of confounding variables revealed that high urinary sodium excretion, higher pretreatment diastolic blood pressure and small sample size were directly related to treatment effect; it also revealed that race and study duration may be important factors.

Prevention of an increase in blood pressure or the development of hypertension through potassium supplementation has been the focus of 2 large prevention studies.[53,54] The Hypertension Prevention Trial[53] randomly assigned 841 men and women to 1 of 4 diets: a low-calorie diet, a low-sodium diet, a combination of these 2 diets, or a low-sodium/high-potassium diet. Patients were assessed at 6 months and again at 3 years. Counselling of the patients assigned to the low-sodium/high-potassium diet resulted in a decrease in sodium intake by approximately 36 mmol/day but no change in potassium intake (as judged by urinary excretion) after 6 months; hence, there was an increase in the urinary sodium-to-potassium ratio. After 3 years, there was no greater reduction in blood pressure in the low-sodium/high-potassium group than in the low-sodium group. The relative importance of the negative result of this trial is unclear; because there was no evidence of an increase in dietary potassium intake over the long term, it is not possible to truly assess the long-term effect of a high-potassium diet on blood pressure. However, these results suggest that people are not able to maintain these dietary changes, which would limit the effectiveness of prescribing high-potassium diets over the long term. The Trial of Hypertension Prevention[54] was a large, short-term, level II trial of 318 patients that demonstrated no effect on blood pressure of a daily intake of 60 mmol of potassium chloride over 6 months. In addition, 4 nonrandomized trials[57–60] have shown inconsistent results, and 2 randomized trials[55,56] of normotensive patients demonstrated no reduction in blood pressure (Table 3). In the DASH trial[49] the diet enhanced with fruits and vegetables did not affect blood pressure in the subgroup of normotensive participants (level III evidence). Despite the suggestive epidemiologic data, intervention trials have failed to demonstrate that potassium supplementation prevents an increase in blood pressure or the development of hypertension.

In these treatment and prevention trials, potassium supplementation was given in addition to a dietary intake that averaged approximately 60 mmol of potassium per day and was shown to be ineffective. This baseline amount of dietary potassium can be obtained by following *Canada's Food Guide to Healthy Eating*,[61] with a focus on fruits and vegetables. Evidence does not support potassium supplementation for normotensive people to prevent an increase in blood pressure, nor for hypertensive patients to reduce blood pressure.

Recommendations

Prevention

- The daily dietary intake of potassium should be 60 mmol or more, because this level of intake has been associated with a reduced risk of stroke-related death (grade D recommendation).
- For normotensive people obtaining on average 60 mmol of potassium daily through dietary intake, potassium supplementation is not recommended as a means of preventing an increase in blood pressure (grade B recommendation).

Treatment

- Potassium supplementation above the recommended daily dietary intake of 60 mmol is not recommended as a treatment for hypertension (grade B recommendation).

Table 3: Prevention studies of potassium supplementation in normotensive subjects

Study design	Subjects	Daily K dose, mmol	Duration	Dietary changes		Change in BP, mm Hg	Comments
				Na	K		
Level II							
Randomized[53]	195	Diet > 100	3 yr	–36	0	No significant reduction with K supplement over that of low Na diet	No significant increase in urinary K after 6 mo
Double-blind placebo-controlled RCT[54]	318	60	6 mo			NS	Urinary Na 150 mmol/d
Double-blind placebo-controlled RCT[55]	44	80	28 d			NS	
Double-blind placebo-controlled RCT[56]	24	75	14 d			NS	Crossover design
Level III							
Randomized[49]	326 of 459	Diet	8 wk			NS	Normotensive subgroup
Single-blind open[57]	20	96	7 d	+9	+95	–4.4/–0.1 NS	
Single-blind open[58]	64	66	4 wk	–3	+23	+0.4/+0.8 NS	
Single-blind crossover[59]	23	100	2 wk	0	+97	–4.2/–4.6*	
Level IV							
Open crossover[60]	20	120	2 wk	–55	+44	–1.7/–4.5†	

*Significant reduction of BP.
†Significant only for reduction of DBP.

Magnesium supplementation

The relation between dietary magnesium and blood pressure has been evaluated in epidemiologic studies (Table 4). Dietary magnesium intake can be estimated using food diaries, food records or food frequency questionnaires. Urinary excretion is not a reliable indicator of ingestion because only a portion of ingested magnesium is absorbed and that amount may not be proportionately excreted through the kidneys.

The Nurses' Health Study[18,21] is a prospective cohort study of major diseases in a large group of nurses (mostly white) in the United States. The dietary intake of several nutrients was assessed using a food frequency questionnaire. Blood pressure was self-reported. The initial 4-year follow-up report[18] stated that a diet high in magnesium was associated with a reduced risk of hypertension (relative risk 0.77). The food frequency questionnaire was "refined" for the second 4-year stage, and no protective effect was seen.[21] The findings of the second stage were consistent with the conclusions of the Physicians' Health Study,[19] in which only dietary fibre intake was associated with a reduction in the relative risk of hypertension. A cross-sectional study from Belgium[62] demonstrated a correlation between magnesium intake and measured blood pressure in women, but not in men. Joffres and colleagues[63] assessed dietary nutrients and measured blood pressure in 615 men in the Honolulu Heart Study. They found a high intercorrelation among many nutrients and blood pressure but could not separate the effects of magnesium from the effects of other nutrients. Therefore, high dietary magnesium intake does not appear to be associated with prevention of hypertension.

Magnesium supplementation for hypertensive people has been tested in intervention trials, but there is no clear evidence of benefit (Table 5).[64–75] Ten level II studies, in which the daily intake of magnesium was 12.5–40 mmol for up to 6 months, showed no effect, but one study[64] demonstrated a modest reduction (by 3.4 mm Hg) in diastolic blood pressure. Sacks and associates[47] gave magnesium in combination with potassium and calcium to 96 patients, but saw no significant effect at 6 months. In the DASH trial[49] there was an increase in urinary excretion of magnesium in participants on the combination diet (low-fat dairy products and fruit and vegetables) consistent with an increase in

Table 4: Epidemiology studies of the relation between dietary magnesium (Mg) and blood pressure or hypertension

Method of assessing dietary Mg	Subjects	Results	Comments
Questionnaire and interview[62]	8 058	Correlation in women only	Cross-sectional study; BP measured
FFQ[18]	58 218 women	Intake < 200 mg/d associated with RR of 0.77 for hypertension over 4 yr	Inverse relation between dietary Mg and BP in normotensive subjects only; findings refuted in follow-up study; BP self-reported
FFQ[19]	30 681 men	No RR with low Mg diet	Inverse relation between dietary Mg and BP in normotensive subjects only; BP self-reported
FFQ[21]	41 541 women	No RR with low Mg diet	Inverse relation between dietary Mg and BP in normotensive subjects only; BP self-reported

Table 5: Treatment studies of magnesium supplementation in hypertensive subjects

Study design	Subjects	Daily Mg supplement, mmol	Duration	Effect on BP, mm Hg SBP	Effect on BP, mm Hg DBP	Comments
Level II						
Double-blind placebo-controlled RCT[64]	91 women	20	6 mo	–2.7	–3.4*	Only DBP change significant
Double-blind placebo-controlled RCT[47]	96	15	6 mo	NS	NS	Combination therapy
Double-blind, placebo-controlled crossover RCT[65]	17	24	1 mo	NS	NS	
Double-blind placebo-controlled RCT[66]	41	12.5	6 mo	NS	NS	
Double-blind placebo-controlled RCT[67]	25	10	8 wk	NS	NS	
Double-blind placebo-controlled RCT[68]	13	40	3 mo	NS	NS	
Double-blind, placebo-controlled crossover RCT[27]	37	20	2 mo	NS	NS	
Double-blind placebo-controlled RCT[69]	71	15	6 mo	NS	NS	
Double-blind placebo-controlled RCT[70]	14	15	6 mo	NS	NS	
Double-blind, placebo-controlled crossover RCT[71]	17	15–40	9 wk	–7.9	–8.2*	At 30 and 40 mmol/d
Double-blind, placebo-controlled crossover RCT[72]	39	15	2 mo	NS	NS	
Double-blind placebo-controlled RCT[73]	21	15.8	3 wk	NS	NS	
Level III						
Nonrandomized[74]	21	15	1 mo	Yes		
Level V						
Open[75]	20	15	6 mo	–12	–8	

*Statistically significant.

dietary intake of this nutrient. It is not clear if the effect of the combination diet in reducing blood pressure was related to increased magnesium intake[49] for either the hypertensive or normotensive participants.

In the Trial of Hypertension Prevention[54] 430 patients were randomly assigned to receive placebo or 15 mmol magnesium per day for 6 months. No beneficial effect was demonstrated.

In summary, the epidemiologic studies have not reliably or consistently shown a relation between magnesium intake and blood pressure or prevention of hypertension. No beneficial effect of supplementation with magnesium has been demonstrated for either the treatment or the prevention of hypertension.

Recommendations

Prevention

- For normotensive people, magnesium supplementation is not recommended as a means of preventing an increase in blood pressure (grade B recommendation).

Treatment

- Magnesium supplementation is not recommended as a treatment for hypertension (grade B recommendation).

Calcium supplementation

Epidemiologic studies have examined the relation between dietary calcium and blood pressure or hypertension. Dietary intake of calcium is estimated in the same way as intake of magnesium, because gastrointestinal absorption of calcium is also incomplete. Reports describing an association between dietary calcium intake and blood pressure have delivered inconsistent messages (Table 6). The initial follow-up report from the Nurses' Health Study[18] demonstrated that a diet high in calcium was associated with a reduced risk of hypertension over 4 years. However, this conclusion was refuted in the second follow-up report.[21] This inconsistency is thought to be related to the refinement of the food frequency questionnaire, which affected estimated dietary intake of calcium, as well as that of magnesium. Reports based on the National Health and Nutrition Examination Surveys (NHANES-1) database have also brought forth discrepancies in analyses and conclusions. McCarron and collaborators[76] reported an inverse correlation between dietary calcium intake and blood pressure, but other analyses[77–79] yielded different conclusions. A report by Sempos and coworkers[80] using the NHANES-1 and NHANES-2 databases demonstrated a lack of association between dietary calcium and blood pressure. Some authors[81–88] have found correlations only within subgroups of their main study populations, which weakens the support for an association. One meta-analysis[89] reported a weak inverse relation between dietary calcium intake and blood pressure. Hamet[90] under-

Table 6: Epidemiology studies of the relation between dietary calcium (Ca) and blood pressur or hypertension

Method of assessing dietary Ca	Subjects	Effect on BP	Comments
FFQ[18]	58 218 women	RR 0.78 for higher Ca intake*	Initial 4-yr follow-up of Nurses Health Study; refuted on follow-up study; BP self-reported
FFQ[19]	30 681 men	NS	Lowered risk only in lean men; BP self-reported
FFQ[21]	41 541 women	NS	4-yr follow-up of nonhypertensive subjects; BP self-reported
Diet recall[76]	10 372	Risk higher if Ca intake low	High Na diet associated with low BP; BP measured
Diet recall[79]	10 361	NS	4-yr follow-up NHANES-1; BP measured
Diet recall[80]	5 840 men, 5 490 women	NS	NHANES-1 and 2; BP measured
Diet recall[14]	8 000	Inconclusive	Intercorrelation between cations limited analysis; BP measured
Diet recall[63]	615 men	NS	BP measured
7-day diet record[81]	387 men	NS	BP measured
Diet record, dietitian[82]	210 men	NS	BP measured
Diet record, blood levels[62]	4 167 men, 3 891 women	Serum Ca related to SBP and DBP*	BP measured
Diet recall, dietitian[83]	7 011 men	NS	Related in group with low alcohol use only; BP measured
24-h urine collection[20]		Inverse relation	BP measured
Diet recall[84]	7 073	NS, except in subgroup	NHANES 5–12-yr follow-up; BP measured
FFQ[85]	6 517 non-black women, > 64 yr	SBP*	1 g Ca = –1.5/+0.5 effect on BP; BP measured
FFQ[86]	5 049	Variable effect depending on diet source of Ca	BP measured
Diet record[87]	182 normotensives	$r = –0.2$*	BP measured
Diet record, dietitian[88]	167 women	NS	10-yr follow-up; BP measured

*Statistically significant.

took an extensive review of the issue but was unable to definitively support a link between calcium intake and hypertension.

In examining the potential effect of calcium supplementation on blood pressure, we reviewed 11 randomized trials and 5 non-randomized trials.[47,91–105] (Table 7). In most studies, there were no significant changes in blood pressure. McCarron and Morris[91] reported a trial that included 48 hypertensive patients randomly assigned to receive placebo or 1 g of calcium daily for 3 weeks. The effects on blood pressure were inconsistent, and the trial was judged to be a "negative" study. Sacks and associates[47] reported no significant effect on blood pressure for 94 patients randomly assigned to receive placebo or combination therapy with either calcium and magnesium or calcium and potassium for 6 months. There have been suggestions that certain patient groups may benefit from calcium supplementation, but there is no trial evidence to support such suggestions. Two meta-analyses of randomized trials[106,107] reported a modest reduction in blood pressure with calcium supplementation, but neither recommended calcium supplementation. Hamet[90] reached a similar conclusion. The recent DASH trial[49] reported that blood pressure declined to a significantly greater extent in the hypertensive subjects who were on a diet that included low-fat dairy products and extra fruit and vegetables than in those who were on either the control diet or the diet high in fruits and vegetables (level III evidence). Presumably this was because of the increase in calcium intake from the dairy products, although there was no significant change in urinary calcium excretion.

Calcium supplementation has not been shown to prevent an increase in blood pressure or hypertension. In the Trial of Hypertension Prevention, 445 normotensive patients were randomly assigned to receive either placebo or 1 g of calcium daily for 6 months. There was no difference in blood pressure between the groups. Three other small studies[91,93,97] included normotensive subjects (in addition to hypertensive patients) and failed to demonstrate any reduction in blood pressure with calcium supplementation. In the DASH study,[49] however, the normotensive subgroup experienced a decrease in blood pressure when eating the diet that included low-fat dairy products and extra fruit and vegetables (level III evidence). Presumably, this effect was related to the increase in dietary calcium, although again there was no change in urinary calcium excretion.

The recommended daily intake for calcium can be obtained by following *Canada's Food Guide to Healthy Eating*,[61] which recommends 2 to 4 servings of milk or milk products daily. Low-fat dairy products, as used in the DASH study, are preferred, to limit an increase in dietary fat. The evidence does not support the use of calcium supplementation as a means of preventing an increase in blood pressure in normotensive people or as a treatment for hypertension.

Recommendations

Prevention

- For normotensive people, calcium supplementation above the recommended daily dietary intake is not recommended as a means of preventing an increase in blood pressure (grade B recommendation).

Treatment

- Calcium supplementation above the recommended daily dietary intake is not recommended as a treatment for hypertension (grade B recommendation).

Table 7: Treatment studies of calcium supplementation in hypertensive subjects

Study design	Subjects	Daily Ca dose	Duration	Effect on BP, mm Hg
Level II				
Double-blind placebo-controlled crossover RCT[91]	48 hypertensive, 32 normotensive	1 g	3 wk	Standing SBP –5.6*; supine SBP –3.8; standing DBP –2.3
Double-blind placebo-controlled RCT[92]	90	1 g	12 wk	NS
Double-blind placebo-controlled RCT[93]	47 hypertensive, 48 normotensive	10 mmol, 20 mmol	8 wk	NS
Double-blind placebo-controlled crossover RCT[94]	23	1 g	8 wk	NS
Double-blind randomized crossover[95]	18	40 mmol	1 mo	NS
Double-blind placebo-controlled crossover[96]	8	1 g	3 wk	NS
Double-blind placebo-controlled crossover RCT[97]	17 hypertensive, 29 normotensive	1.5 g	8 wk	NS (overall)
Double-blind placebo-controlled crossover RCT[98]	26	800 mg	8 wk	NS
Double-blind placebo-controlled crossover RCT[99]	15	400 mg and 1400 mg	8 wk each	NS
Double-blind placebo-controlled crossover RCT[100]	19	1200 mg	6 mo	NS
Double-blind placebo-controlled RCT [47]	94	500 mg†	6 mo	NS
Level III				
Single-blind placebo-controlled[101]	103	1 g	12 wk	NS
Open[102]	6+5	400 mg, 1400 mg by diet	6 wk for each diet	DBP –8 on low Ca*
Double-blind placebo-controlled crossover RCT[103]	18	1 g	15 wk	Standing SBP –8.6*
Crossover[104]	13 men	400 mg v. 1500 mg	4 wk	NS
Single-blind placebo-controlled[105]	8 hypertensive, 8 normotensive	800 mg	8 d	NS

*Statistically significant.
†Combined with K or Mg.

The recommendations on potassium, magnesium and calcium are summarized in Tables 8–10.

Interpretation

In the epidemiologic literature, several cross-sectional and prospective cohort studies have not supported a definitive link between the dietary intake of potassium, magnesium, or calcium and blood pressure or hypertension. Initial supportive evidence has been superseded by subsequent negative results in 2 large prospective studies after the method used to estimate dietary cation intake was revised. The method of assessing the blood pressure of participants in these reports was variable: some studies used direct measurements, and others relied on patients to recall their blood pressure as measured in a physician's office. These variations in methodology for determining both dependent and independent variables undermine the quality of the evidence and the conclusions that can be drawn from it.

The intervention studies are similarly variable. With the "levels-of-evidence" methodology, long-term, randomized controlled trials are the basis for developing recommendations. Since there are few such studies, the recommendations may reflect the results of only one, albeit methodologically strong, study. Short-term studies that use dietary or multiple manipulations are more likely to reflect a real-life strategy for enhancing cation intake, but because they are shorter in length they are not usually used as a basis for recommendations. To date, no long-term studies have evaluated the effect of the increased intake of any of these cations on morbidity and mortality rates.

Table 8: Recommendations for potassium intake and supplementation

Recommendation	Grade
Prevention	
A dietary intake of 60 mmol potassium per day or more over the long-term is recommended because this level of intake has been associated with a reduced risk of stroke-related death	D
Potassium supplementation is not recommended for normotensive people to prevent an increase in blood pressure over the short-term when given in addition to an average dietary intake of 60 mmol per day	B
Treatment	
Potassium supplementation is not recommended as a treatment for hypertension when given in addition to an average dietary intake of 60 mmol per day	B

Table 9: Recommendations for magnesium supplementation

Recommendation	Grade
Prevention	
Magnesium supplementation is not recommended for normotensive people to prevent an increase in blood pressure	B
Treatment	
Magnesium supplementation is not recommended as a treatment for hypertension	B

Table 10: Recommendations for calcium supplementation

Recommendation	Grade
Prevention	
Calcium supplementation is not recommended for normotensive people to prevent an increase in blood pressure when given in addition to recommended daily dietary intake	B
Treatment	
Calcium supplementation is not recommended as a treatment for hypertension when given in addition to recommended daily dietary intake	B

The recommendations developed from our evaluation of the literature using levels of evidence may differ from those developed through meta-analysis. However, the meta-analyses of potassium supplementation[51,52] did not support its use in the treatment of hypertensive patients nor to prevent hypertension in those at risk for this condition; this is consistent with our recommendation against potassium supplementation. However, potassium supplementation may be effective in distinct groups of patients, such as those with diuretic-induced hypokalemia, those of African ancestry and those who have low dietary potassium intake. Two meta-analyses[106,107] and an extensive review of the literature on calcium supplementation and hypertension[90] did not recommend calcium supplementation because the effect was very small and not clinically meaningful.

A question has been raised concerning the definition of "nonpharmacologic management": Is nutrient supplementation in capsule form a truly nonpharmacologic method, or does it represent a change in diet? For the purposes of this review, studies that used any oral means of augmenting cation intake were included. Some studies changed the intake of more than one cation, which makes it difficult, if not impossible, to determine the effect of a change in a single cation. Dietary change also presents challenges: What additional amounts of which cations were delivered by the dietary change, and which contributed to the blood pressure responses? Changes in the diet to increase the intake of potassium, magnesium or calcium, or any combination of these, may result in changes to other components of the diet, such as sodium, fat or fibre (from fruits, vegetables and cereal grains); these changes may also have a beneficial effect on body weight and on blood cholesterol and antioxidant levels, other factors thought to influence blood pressure in hypertensive patients[108] and morbidity and death from cardiovascular disease.

For the purpose of formulating these recommendations, we assumed that people consume a diet consistent with the recommendations in *Canada's Food Guide to Healthy Eating*.[61] Such a diet would provide approximately 60 mmol of potassium and 1 g of calcium per day. Baseline cation intake may be an important factor determining the response to supplementation. As suggested in some of the work on potassium supplementation,[31,50] the response to supplementation will probably depend on whether the subject is fol-

lowing a deficient diet at baseline; hence a dietary history may be needed for all subjects. Overall, patients should be encouraged to follow a healthy diet.

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References

1. Priddle WW. Observations on the management of hypertension. *CMAJ* 1931;25:5-8.
2. Campbell NRC, Burgess E, Choi BCK, Taylor G, Wilson E, Cléroux J, et al. Lifestyle modifications to prevent and control hypertension: 1. Methods and an overview of the Canadian recommendations. *CMAJ* 1999;160(Suppl 9):S1-6.
3. Carruthers SG, Larochelle P, Haynes RB, Petrasovits A, Schiffrin EL. Report of the Canadian Hypertension Society consensus conference: 1. Introduction. *CMAJ* 1993;149(3):289-93.
4. Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality. A 12-year prospective population study. *N Engl J Med* 1987;316:235-40.
5. Walker WG, Whelton PK, Saito H, Russell RP, Hermann J. Relation between blood pressure and renin, renin substrate, angiotensin II, aldosterone and urinary sodium and potassium in 574 ambulatory subjects. *Hypertension* 1979;1:287-91.
6. Watson RL, Langford HG, Abernethy J, Barnes TY, Watson MJ. Urinary electrolytes, body weight, and blood pressure. Pooled cross-sectional results among four groups of adolescent females. *Hypertension* 1980;2(Suppl I):I93-8.
7. Grim CE, Luft FC, Miller JZ, Meneely GR, Battarbee HD, Hames CG, et al. Racial differences in blood pressure in Evans County, Georgia: relationship to sodium and potassium intake and plasma renin activity. *J Chron Dis* 1980;33:87-94.
8. Lever AF, Beretta-Piccoli C, Brown JJ, Davies DL, Fraser R, Robertson JIS. Sodium and potassium in essential hypertension. *BMJ* 1981;283:463-8.
9. Ophir O, Peer G, Gilad J, Blum M, Aviram A. Low blood pressure in vegetarians: the possible role of potassium. *Am J Clin Nutr* 1983;37:755-62.
10. Khaw KT, Barrett-Connor E. Dietary potassium and blood pressure in a population. *Am J Clin Nutr* 1984;39:963-8.
11. Dai WS, Kuller LH, Miller G. Arterial blood pressure and urinary electrolytes. *J Chron Dis* 1984;37:75-84.
12. Kihara M, Fujikawa J, Ohtaka M, Mano M, Nara Y, Horie R, et al. Interrelationships between blood pressure, sodium, potassium, serum cholesterol, and protein intake in Japanese. *Hypertension* 1984;6:736-42.
13. Frisancho AR, Leonard WR, Bollettino LA. Blood pressure in blacks and whites and its relationship to dietary sodium and potassium intake. *J Chron Dis* 1984;37:515-9.
14. Reed D, McGee D, Yano K, Hankin J. Diet, blood pressure, and multicollinearity. *Hypertension* 1985;7:405-10.
15. Smith WCS, Crombie IK, Tavendale RT, Gulland SK, Tunstall-Pedoe HD. Urinary electrolyte excretion, alcohol consumption, and blood pressure in the Scottish heart health study. *BMJ* 1988;297:329-30.
16. INTERSALT Cooperative Research Group. INTERSALT: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *BMJ* 1988;297:319-28.
17. Khaw KT, Barrett-Connor E. The association between blood pressure, age, and dietary sodium and potassium: a population study. *Circulation* 1988;77:53-61.
18. Witteman JCM, Willett WC, Stampfer MJ, Colditz GA, Sacks FM, Speizer FE, et al. A prospective study of nutritional factors and hypertension among US women. *Circulation* 1989;80:1320- 7.
19. Ascherio A, Rimm EB, Giovannucci EL, Colditz GA, Rosner B, Willett WC, et al. A prospective study of nutritional factors and hypertension among US men. *Circulation* 1992;86:1475-84.
20. Lai S, Yuanchang T, Weiling H, Peisheng M, Guanqing H. Urinary electrolyes and blood pressure in three Yi farmer populations, China. *Hypertension* 1989;13:22-30.
21. Ascherio A, Hennekens C, Willett WC, Sacks F, Rosner B, Manson J, et al. Prospective study of nutritional factors, blood pressure, and hypertension among US women. *Hypertension* 1996;27:1065-72.
22. Grimm RH, Neaton JD, Elmer PJ, Svendsen KH, Levin J, Segal M, et al. The influence of oral potassium on blood pressure in hypertensive men on a low-sodium diet. *N Engl J Med* 1990;322:569-74.
23. Medical Research Council Working Party. Comparison of the antihypertensive efficacy and adverse reactions of two doses of bendrofluazide and hydrochlorothiazide and the effect of potassium supplementation on the hypotensive action of bendrofluazide: substudies of the Medical Research Council's trial of treatment of mild hypertension. *J Clin Pharmacol* 1987;27:271-7.
24. Langford HG, Davis BR, Blaufox D, Oberman A, Wassertheil-Smoller S, Hawkins M, et al. Effect of drug and diet treatment of mild hypertension on diastolic blood pressure. *Hypertension* 1991;17:210-7.
25. Grimm RH, Kofron PM, Neaton JD, Svendson KH, Elmer PJ, Holland L, et al. Effect of potassium supplementation combined with dietary sodium reduction on blood pressure in men taking anti-hypertensive medication. *J Hypertens* 1988;6(Suppl 4):S591-3.
26. Siani A, Strazzullo P, Giacco A, Pacioni D, Celentano E, Mancini M. Increasing the dietary potassium intake reduces the need for antihypertensive medications. *Ann Intern Med* 1991;115:753-9.
27. Patki PS, Singh P, Gokhale SV, Bulakh PM, Shrotri DS, Patwardham B. Effect of potassium and magnesium in essential hypertension: a double blind, placebo controlled crossover study. *BMJ* 1990;301:521-3.
28. Obel AO. Placebo-controlled trial of potassium supplements in black patients with mild essential hypertension. *J Cardiovasc Pharmacol* 1989;14:294-6.
29. Siani A, Strazzullo P, Russo L, Guglielmi S, Iacoviello L, Ferrara LA, et al. Controlled trial of long term oral potassium supplements in patients with mild hypertension. *BMJ* 1987;294:1453-6.
30. Svetky LP, Yarger WE, Feussner JR, DeLong E, Klotman PE. Double-blind, placebo-controlled trial of potassium chloride in the treatment of mild hypertension. *Hypertension* 1987;9:444-50.
31. Matlou SM, Isles CG, Higgs A, Milne FJ, Murray GD, Schultz E, et al. Potassium supplementation in blacks with mild to moderate essential hypertension. *J Hypertens* 1986;4:61-4.
32. Grobbee DE, Hofman A, Roelandt JT, Boomsma F, Schalekamp MA, Valkenburg HA. Sodium restriction and potassium supplementation in young people with mildly elevated blood pressure. *J Hypertens* 1987;5:115-9.
33. Kaplan NM, Carnegie A, Raskin P, Heller JA, Simmons M. Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. *N Engl J Med* 1985;312:746-9.
34. Richards AM, Nicholls MG, Espiner EA, Ikram H, Maslowski AH, Hamilton EJ, et al. Blood-pressure response to moderate sodium restriction and to potassium supplementation in mild essential hypertension. *Lancet* 1984;2:757-61.
35. Smith SJ, Markandu ND, Sagnella GA, MacGregor GA. Moderate potassium chloride supplementation in essential hypertension: Is it additive to moderate sodium restriction? *BMJ* 1985;290:110-3.
36. MacGregor GA, Smith SJ, Markandu ND, Banks RA, Sagnella GA. Moderate potassium supplementation in essential hypertension. *Lancet* 1982;2:567-70.
37. Valdes G, Vio CP, Montera J, Avendano R. Potassium supplementation lowers blood pressure and increases urinary kallikein in essential hypertensives. *J Hum Hypertens* 1991;5:91-6.
38. Fotherby MD, Potter JF. Potassium supplementation reduces clinic and ambulatory blood pressure in elderly hypertensive patients. *J Hypertens* 1992;10:1403-8.
39. Khaw KT, Thom S. Randomized double-blind cross-over trial of potassium on blood-pressure in normal subjects. *Lancet* 1982;2:1127-8.
40. Zoccali C, Cumming AMM, Hutcheson MJ, Barnett P, Semple PF. Effects of potassium on sodium balance, renin, noradrenaline and arterial pressure. *J Hypertens* 1985;3:67-72.
41. Overlack AO, Conrad H, Stumpe KO. The influence of oral potassium citrate/bicarbonate on blood pressure in essential hypertension during unrestricted salt intake. *Klin Wochenschr* 1991;69(Suppl 25):79-83.
42. Smith SR, Klotman PE, Svetlkey LP. Potassium chloride lowers blood pressure and causes natriuresis in older patients with hypertension. *J Am Soc Nephrol* 1992;2:1302-9.
43. Iimura O, Kijima T, Kikuchi K, Miyama A, Ando T, Nakao T, et al. Studies on the hypotensive effect of high potassium intake in patients with essential hypertension. *Clin Sci* 1981;61:77s-80s.
44. Overlack A, Muller HM, Kolloch R, Ollig A, Moch B, Kleinmann R, et al. Long-term antihypertensive effect of oral potassium in essential hypertension. *J Hypertens* 1983;1(Suppl 2):S165- 7.
45. Smith SJ, Markandu ND, Sagnella GA, Poston L, Hilton PJ, MacGregor GA. Does potassium lower blood pressure by increasing sodium excretion? A metabolic study in patients with mild to moderate essential hypertension. *J Hypertens* 1983;1(Suppl 2):S27-30.
46. Chalmers J, Morgan T, Doyle A, Dickson B, Hopper J, Mathews J, et al. Australian National Health and Medical Research Council dietary salt study in mild hypertension. *J Hypertens* 1986;4(Suppl 6):S629-7.
47. Sacks FM, Brown LE, Appel L, Borhani NO, Evans D, Whelton P. Combinations of potassium, calcium, and magnesium supplements in hypertension. *Hypertension* 1995;26(6 Pt 1):950-6.

48. Geleijnse JM, Witteman JCM, Bak AAA, den Breeijen JN, Grobbee DE. Reduction in blood pressure with a low sodium, high potassium, high magnesium salt in older subjects with mild to moderate hypertension. *BMJ* 1994;309:436-40.
49. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997;336:1117-24.
50. Brancati FL, Appel LJ, Seidler AJ, Whelton PK. Effect of potassium supplementation on blood pressure in African Americans on a low-potassium diet. A randomized, double-blind, placebo-controlled trial. *Arch Intern Med* 1996;156:61-7.
51. Cappuccio FP, MacGregor GA. Does potassium supplementation lower blood pressure? A meta-analysis of published trials. *J Hypertens* 1991;9:465-73.
52. Whelton PK, He J, Cutler JA, Brancati FI, Appel LJ, Follmann D, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA* 1997;277:1624-32.
53. Hypertension Prevention Trial Research Group. The Hypertension Prevention Trial: three-year effects of dietary changes on blood pressure. *Arch Intern Med* 1990;150:153-62.
54. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, phase I [published erratum appears in *JAMA* 1992;267(17):2330]. *JAMA* 1992;267:1213-20.
55. Barden AE, Vandongen R, Beilin LJ, Margets B, Rogers P. Potassium supplementation does not lower blood pressure in normotensive women. *J Hypertens* 1986;4:339-43.
56. Mullen JT, O'Connor DT. Potassium effects on blood pressure: Is the conjugate anion important? *J Hum Hypertens* 1990;4:589-96.
57. Weissberg PL, West MJ, Kendall MJ, Ingram M, Woods KL. Effect of changes in dietary sodium and potassium on blood pressure and cellular electrolyte handling in young normotensive subjects. *J Hypertens* 1985;3:475-80.
58. Miller JZ, Weinberger MH, Christian JC. Blood pressure response to potassium supplementation in normotensive adults and children. *Hypertension* 1987;10:437-42.
59. Parfrey PS, Vandenburg MJ, Wright P. Blood pressure and hormonal changes following alteration in dietary sodium and potassium in mild essential hypertension. *Lancet* 1981;1:113-7.
60. Skrabal F, Aubock J, Hortnagi H. Low sodium/high potassium diet for prevention of hypertension: probable mechanism of action. *Lancet* 1981;2:895-900.
61. *Canada's food guide to healthy eating*. Ottawa: Health and Welfare Canada; 1992. Cat no. H39-252/1992E.
62. Kesteloot H, Joossens JV. Relationship of dietary sodium, potassium, calcium, and magnesium with blood pressure. Belgian interuniversity research on nutrition and health. *Hypertension* 1988;12:594-9.
63. Joffres MR, Reed DM, Yano K. Relationship of magnesium intake and other dietary factors to blood pressure: the Honolulu Heart Study. *Am J Clin Nutr* 1987;45:469-75.
64. Witteman JCM, Grobbee DE, Derkx FHM, Bouillon R, de Bruijn AM, Hofman A. Reduction of blood pressure with oral magnesium supplementation in women with mild to moderate hypertension. *Am J Clin Nutr* 1994;60:129-35.
65. Cappuccio FP, Markandu ND, Beynon GW, Shore AC, Sampson B, MacGregor GA. Lack of effect of oral magnesium on high blood pressure: a double blind study. *BMJ* 1985;291:235-8.
66. Henderson DG, Schierup J, Schodt T. Effect of magnesium supplementation on blood pressure and electrolyte concentration in hypertensive patients receiving long term diuretic treatment. *BMJ* 1986;293:664-5.
67. Nowson CA, Morgan TO. Magnesium supplementation in mild hypertensive patients on a moderately low sodium diet. *Clin Exp Pharmacol Physiol* 1989;16:299-302.
68. Zemel PC, Zemel MB, Urberg M, Douglas FL, Geiser R, Sowers JR. Metabolic and hemodynamic effects of magnesium supplementation in patients with essential hypertension. *Am J Clin Nutr* 1990;51:665-9.
69. Lind L, Lithell H, Pollare T, Ljunghall S. Blood pressure response during long-term treatment with magnesium is dependent on magnesium status. *Am J Med* 1991;4:674-9.
70. Ferrara LA, Iannuzzi R, Castaldo A, Iannuzzi A, Dello Russo A, Mancini M. Long-term magnesium supplementation in essential hypertension. *Gen Cardiol* 1992;81:25-33.
71. Widman L, Wester PO, Stegmayr BK, Wirell M. The dose-dependent reduction in blood pressure through administration of magnesium — a double blind placebo controlled cross-over study. *Am J Hypertens* 1993;6:41-5.
72. Wirell NP, Wester PO, Stegmayr BG. Nutritional dose of magnesium in hypertensive patients on beta-blockers lowers systolic blood pressure: a double-blind cross-over study. *J Intern Med* 1994;236:189-95.
73. Reyes AJ, Leary WP, Acosta-Barrios TN, Davis WH. Magnesium supplementation in hypertension treated with hydrochlorthiazide. *Curr Ther Res* 1984;36:332-40.
74. Motoyama T, Sano H, Suzuki H, Kawavuchi K, Saito K, Furuta Y, et al. Oral magnesium treatment and the erythrocyte sodium pump in patients with essential hypertension. *J Hypertens* 1986;4(Suppl 6):S682-4.
75. Dyckner T, Wester PO. Effect of magnesium on blood pressure. *BMJ* 1983;286:1847-49.
76. McCarron DA, Morris CD, Henry HJ, Stanton JL. Blood pressure and nutrient intake in the United States. *Science* 1984;224:1392-8.
77. Feinlieb M, Lenfant C, Miller SA. Hypertension and calcium. *Science* 1984;225:385-6.
78. Gruchow HW, Sobocinski KA, Barboriak JJ. Alcohol, nutrient intake, and hypertension in US adults. *JAMA* 1985;253:1567-70.
79. Gruchow HW, Sobocinski KA, Barboriak JJ. Calcium intake and the relationship of dietary sodium and potassium to blood pressure. *Am J Clin Nutr* 1988;48:1463-70.
80. Sempos C, Cooper R, Kovar MG, Johnson C, Drizd T, Yetley E. Dietary calcium and blood pressure in National Health and Nutrition Examination Surveys I and II. *Hypertension* 1986;8:1067-74.
81. Elliott P, Fehily AM, Sweetnam PM, Yarnell JWG. Diet, alcohol, body mass, and social factors in relation to blood pressure: the Caerphilly Heart Study. *J Epidemiol Community Health* 1987;41:37-43.
82. Fodor JG, Rusted IE. Electrolyte profiles in a Newfoundland population: the Newfoundland study. *Clin Invest Med* 1987;10:586-91.
83. Criqui MH, Langer RD, Reed DM. Dietary alcohol, calcium, and potassium — independent and combined effects on blood pressure. *Circulation* 1989;80:609-14.
84. Ford ES, Cooper RS. Risk factors for hypertension in a national cohort study. *Hypertension* 1991;18:598-606.
85. Simon JA, Browner WS, Tao JL, Hulley SB. Calcium intake and blood pressure in elderly women. *Am J Epidemiol* 1992;136:1241-7.
86. Trevisan M, Krogh V, Farinaro E, Panico S, Mancini M. Calcium-rich foods and blood pressure: findings from the Italian National Research Council Study (the Nine Communities Study). *Am J Epidemiol* 1988;127:1155-63.
87. Hamet P, Daignault-Gelinas M, Lambert J, Ledoux M, Whissel-Cambiotti L, Bellavance F, et al. Epidemiological evidence of an interaction between calcium and sodium intake impacting on blood pressure — a Montreal study. *Am J Hypertens* 1992;5:378-85.
88. van Beresteijn ECH, Riedstra M, van der Wel A, Schouten EG, Burema J, Kok FJ. Habitual dietary calcium intake and blood pressure change around the menopause: a longitudinal study. *Int J Epidemiol* 1992;21:683-9.
89. Capuccio FP, Elliott P, Allender PS, Pryer J, Follman DA, Cutler JA. Epidemiologic association between dietary calcium intake and blood pressure: a meta-analysis of published data. *Am J Epidemiol* 1995;142:935-45.
90. Hamet P. The evaluation of the scientific evidence for a relationship between calcium and hypertension. *J Nutr* 1995;125(Suppl 2):311S-400S.
91. McCarron DA, Morris CA. Blood pressure response to oral calcium in persons with mild to moderate hypertension. *Ann Intern Med* 1985;103:825-31.
92. Grobbee D, Hofman A. Effect of calcium supplementation on diastolic blood pressure in young people with mild hypertension. *Lancet* 1986;2:703-6.
93. Nowson C, Morgan T. Effect of calcium carbonate on blood pressure in normotensive and hypertensive people. *Hypertension* 1989;13:630-9.
94. Zoccali C, Mallamaci F, Delfino D, Ciccarelli M, Parlongo S, Iellamo D, et al. Double-blind randomized, crossover trial of calcium supplementation in essential hypertension. *J Hypertens* 1988;6:451-5.
95. Cappuccio FP, Markandu ND, Singer DRJ, Smith SJ, Shore AC, MacGregor GA. Does oral calcium supplementation lower high blood pressure? A double blind study. *J Hypertens* 1987;5:67-71.
96. Siani A, Strazzullo P, Guglielmi S, Mancini M. Clinical studies of the effects of different oral calcium intakes in essential hypertension. *J Hypertens* 1987;5(Suppl 5):S311-3.
97. Weinberger MH, Wagner UL, Fineberg NS. The blood pressure effects of calcium supplementation in humans of known sodium responsiveness. *Am J Hypertens* 1993;6:799-805.
98. Meese RB, Gonzales DG, Casparian JM, Ram CVS, Pak CM, Kaplan NM. The inconsistent effects of calcium supplements upon blood pressure in primary hypertension. *Am J Med Sci* 1987;294:219-24.
99. Siani A, Srazzullo P, Guglielmi S, Pacioni D, Giacco A, Iacone R, et al. Controlled trial of low calcium versus high calcium intake in mild hypertension. *J Hypertens* 1988;6:253-6.
100. Tanji JL, Lew EY, Wong GY, Treguboff C, Ward JA, Amsterdam EA. Dietary calcium supplementation as a treatment for mild hypertension. *J Am Board Fam Pract* 1991;4:145-50.
101. Morris CA, McCarron DA. Effect of calcium supplementation in an older population with mildly increased blood pressure. *Am J Hypertens* 1992;5:230-37.
102. Levey WA, Manore MM, Vaughan LA, Carroll SS, VanHalderen L, Felicetta J. Blood pressure responses of white men with hypertension to two low-sodium metabolic diets with different levels of dietary calcium. *J Am Diet Assoc* 1995;95:1280-7.
103. Strazzullo P, Siani A, Guglielmi S, DiCarlo A, Galletti F, Cirillo M, et al. Controlled trial of long-term oral calcium supplementation in essential hypertension. *Hypertension* 1986;8:1084-8.
104. Kynast-Gales SA, Massey LK. Effects of dietary calcium from dairy products on ambulatory blood pressure in hypertensive men. *J Am Diet Assoc* 1992;92:1497-501.
105. Luft FC, Aranoff GR, Sloan RS, Fineberg NS, Weinberger MH. Short-term augmented calcium intake has no effect on sodium homeostasis. *Clin Pharmacol Ther* 1986;39:414-9.
106. Bucher HC, Cook RJ, Guyatt GH, Lang JD, Cook DJ, Hatala R, et al. Effects of dietary calcium supplementation on blood pressure — a meta-analysis of randomized trials. *JAMA* 1996;275:1016-22.
107. Allender PS, Cutler JA, Follmann D, Cappuccio FP, Pryer J, Elliot P. Dietary calcium and blood pressure: a meta-analysis of randomized clinical trials. *Ann Intern Med* 1996;124:825-31.
108. McCarron DA. Role of adequate dietary calcium intake in the prevention and management of salt-sensitive hypertension. *Am J Clin Nutr* 1997;65(Suppl 1):712S-716S.

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