

The Role of Magnesium in Hypertension and Cardiovascular Disease

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Magnesium intake of 500 mg/d to 1000 mg/d may reduce blood pressure (BP) as much as 5.6/2.8 mm Hg. However, clinical studies have a wide range of BP reduction, with some showing no change in BP. The combination of increased intake of magnesium and potassium coupled with reduced sodium intake is more effective in reducing BP than single mineral intake and is often as effective as one antihypertensive drug in treating hypertension. Reducing intracellular sodium and calcium while increasing intracellular magnesium and potassium improves BP response. Magnesium also increases the effectiveness of all antihypertensive drug classes. It remains to be conclusively proven that cardiovascular disease such as coronary heart

disease, ischemic stroke, and cardiac arrhythmias can be prevented or treated with magnesium intake. Preliminary evidence suggests that insulin sensitivity, hyperglycemia, diabetes mellitus, left ventricular hypertrophy, and dyslipidemia may be improved with increased magnesium intake. Various genetic defects in magnesium transport are associated with hypertension and possibly with cardiovascular disease. Oral magnesium acts as a natural calcium channel blocker, increases nitric oxide, improves endothelial dysfunction, and induces direct and indirect vasodilation. *J Clin Hypertens (Greenwich)*. 2011;13:843-847. ©2011 Wiley Periodicals, Inc.

Hypertension remains the leading cause of cardiovascular disease (CVD), affecting approximately 1 billion individuals worldwide.¹ More than 72 million Americans, or nearly 1 in 3 adults, are estimated to have high blood pressure (BP), but only 35% reach goal BP control.² Nearly 70 million more adults are at risk for developing prehypertension, and 90% of adults will probably develop high BP by the age of 65, especially systolic hypertension.³ Hypertension is associated with an increased risk of morbidity and mortality from cerebrovascular accidents (CVA), coronary heart disease (CHD), congestive heart failure, and end-stage renal disease (ESRD). Due to its high prevalence, hypertension remains the most common reason for visits to physician's offices and the primary reason for prescription drug use in the United States.

DIET IN THE PREVENTION AND TREATMENT OF HYPERTENSION

Several epidemiologic studies suggest that diet plays an important role in determining BP.⁴⁻⁶ Dietary therapies known to lower BP include reduced sodium intake, increased potassium and magnesium intake, possibly an increase in calcium intake, and a diet rich in fruits and vegetables.⁴⁻⁶ The landmark Dietary Approaches to Stop Hypertension (DASH) trial demonstrated that modification of diet significantly lowered BP in patients with stage 1 hypertension and high-normal BP.^{7,8} The DASH diet, which emphasizes the consumption of fruits, vegetables, high fiber, and low-fat dairy products, also lowers BP in persons with isolated

systolic hypertension (ISH).⁹ These BP-lowering effects were seen in 8 weeks and were sustained throughout the study period. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines as well as the recent American Heart Association (AHA) recommendations for the prevention and management of CVD and numerous other international organizations also recognize the role that various foods, macronutrients, micronutrients, and minerals play in lowering BP.^{10,12-14}

EFFECT OF MAGNESIUM ON BP

Epidemiologic, observational, and clinical trial data show that a diet high in magnesium (at least 500–1000 mg/d) lowers BP, but the results are inconsistent.¹⁵⁻¹⁷ These varied results may relate to the population studied, duration of the trial, use of concomitant drugs, other nutrients and minerals, type and dose of magnesium administered, pretreatment magnesium level, pretreatment BP level, inadequate monitoring for adherence, use of varied measures of serum magnesium, intracellular magnesium, or 24-hour urinary magnesium excretion, as well as lack of evaluation of baseline plasma renin activity, essential fatty acid status, and genetic magnesium transporter status. In most epidemiologic studies, an inverse relationship has been shown between dietary magnesium intake and BP.¹⁵⁻¹⁷

In a study of 60 patients with hypertension given magnesium oxide at 20 mmol/d during 8 weeks, significant reductions in ambulatory, home, and office BP were observed.¹⁸ The office BP fell by 3.7/1.7 mm Hg, 24-hour ambulatory BP was reduced by 2.5/1.4 mm Hg, and home BP decreased by 2.0/1.4 mm Hg. The levels of serum and urinary magnesium correlated with the BP reduction. Patients with the highest BP levels at entry had the largest reduction in BP.

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Witteaman and colleagues¹⁹ demonstrated significant decreases in BP in a double-blind placebo-controlled trial of 91 middle-aged to elderly women with mild to moderate hypertension using magnesium aspartate-HCl (20 mmol/d or 485 mg of magnesium) for 6 months. There was a significant decrease in systolic BP and diastolic BP by 2.7 mm Hg ($P<.18$) and 3.4 mm Hg ($P<.003$), respectively. In addition, BP response was not associated with baseline magnesium level, and patients taking magnesium had a 50% increase in urinary magnesium excretion. In another study of 48 patients with mild uncomplicated hypertension, those given magnesium 600 mg/d with lifestyle changes vs those with lifestyle changes only had significant reductions in 24-hour systolic BP and diastolic BP during daytime and nighttime readings of 5.6/2.8 mm Hg vs 1.3/1.8 mm Hg ($P<.001$ and $P<.002$, respectively), increased serum and intracellular magnesium, increased urinary magnesium excretion, and decreased intracellular calcium and sodium levels.²⁰ Magnesium supplementation (with calcium and potassium) was administered to 96 patients with hypertension during 6 months by Sacks and colleagues²¹ but no significant reduction in BP was noted.

Meta-analysis of magnesium supplementation has also revealed conflicting results. A review of 29 studies of magnesium was inconclusive as a result of flaws in methodology but suggested that a negative association of BP with magnesium was not present.²² In contrast, a meta-analysis of 20 randomized clinical trials with a median intake of 15.4 mmol/d of magnesium revealed a dose-dependent BP reduction with magnesium supplementation.¹⁵ A more recent meta-analysis of 105 trials randomizing 6805 participants with at least 8 weeks of follow-up found no evidence that magnesium supplements had any important effect on BP.²³

The BP response to magnesium may be dependent in part on the baseline plasma renin activity (PRA), but this has not been verified in subsequent studies.²⁴ Seventeen inpatients with untreated uncomplicated mild to moderate hypertension and 8 age-matched controls were given 1.0 g/d of magnesium oxide for 2 weeks.

The average mean 24-hour BP for both daytime and nighttime readings fell from 104.3 mm Hg to 99.5 mm Hg ($P<.05$) while there was no change in BP in the control group. The PRA was significantly higher in the responder group than the nonresponder group in those who received the magnesium supplement ($P<.05$). Magnesium suppresses circulating Na+K+ ATPase inhibitory activity to attenuate vascular tone and lower BP. Other studies have shown that oral magnesium improves borderline hypertension.²⁵

Magnesium may have a more pronounced BP-lowering effect when administered with high potassium intake and low sodium intake.^{26,27} In a double-blind, randomized, placebo-controlled, crossover trial of 32 weeks' duration, 37 adults with mild to moderate hypertension (diastolic BP <110 mm Hg) were given placebo or potassium 60 mmol/d alone or in combination with magnesium 20 mmol/d in a crossover design. None of the patients were taking any other medications or supplements. The potassium/magnesium combination significantly reduced BP ($P<.001$), but the addition of magnesium to the potassium did not decrease BP further. Other studies suggest that high potassium, high magnesium, and low sodium intake will result in additive reductions in BP²⁷ (Table).

Magnesium given in conjunction with taurine lowers BP, improves insulin resistance, retards atherogenesis, prevents arrhythmias, and stabilizes platelets.^{28,29} The actions may be related to the common mechanism of action of magnesium and taurine to reduce intracellular calcium and sodium levels.^{28,29} In the World Health Organization's Coordinated Cardiovascular Diseases and Alimentary Comparison (WHO-CARDIAC) study, patients with higher 24-hour urine magnesium/creatinine and taurine/creatinine levels had significantly lower cardiovascular risks, including CVA, CHD, and myocardial infarction.²⁹

Magnesium is also effective in further reducing BP in stage I hypertension, diabetes mellitus, and pregnancy when coadministered with antihypertensive agents such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, β -blockers, methyldopa, and other

TABLE. Summary of Clinical Trials and Meta-Analysis of Magnesium Effect on BP

Reference	Dose Mg++	Patients	Duration	Office BP mm Hg	24-h ABPM
18	20 mmol	60	8 wk	3.7/1.7	2.5/1.4
19	20 mmol	91	6 mo	2.7/3.4	
20	600 mg	48			5.6/2.8
21		96	6 mo	No change	
22	Meta-analysis of 29 studies			No change	
15	Meta-analysis of 20 studies with an average mg intake 15.4 mmol. Dose-dependent reduction in BP				
23	Meta-analysis of 105 studies with 6805 patients during an average of 8 wk. No change in BP				
24	1000 mg	17	2 wk	MAP 4.8	
26	20 mmol Potassium chloride 60 mmol	37	32 wk	No change with magnesium but reduction with potassium	

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; MAP, mean arterial pressure; mg, magnesium.

pharmacologic agents.^{30–33} A comprehensive analytic review of 44 human studies of oral magnesium for hypertension showed that magnesium supplements enhanced the BP-lowering effect of antihypertensive medications.³¹

Magnesium intake is correlated with reductions in CVA, CVD, arrhythmias, insulin resistance, diabetes mellitus, and left ventricular hypertrophy in most^{34–38} but not all studies.³⁹ In a study of 34,670 women, cerebral infarction was inversely correlated with both magnesium and potassium intake.³⁴ Left ventricular hypertrophy and left ventricular mass are lower in patients with higher magnesium intakes.³⁵ In the Atherosclerosis Risk in Communities Study (ARIC), higher serum magnesium and magnesium intake were associated with lower prevalence of hypertension, diabetes, and ischemic CVA during 15 years in both men and women.³⁶ Magnesium intake is also correlated with reductions in serum lipids, hyperglycemia, metabolic syndrome, obesity, insulin resistance, and diabetes mellitus.^{37,38}

MECHANISMS OF BP REDUCTION WITH MAGNESIUM

One of the mechanisms by which magnesium lowers BP is by acting like a natural calcium channel blocker. Magnesium competes with sodium for binding sites on vascular smooth muscle cells, increases prostaglandin E, binds to potassium in a cooperative manner, induces endothelial-dependent vasodilation, improves endothelial dysfunction in hypertensive and diabetic patients, decreases intracellular calcium and sodium, and reduces BP.^{28,29,40} Magnesium is more effective in reducing BP when administered as multiple minerals in a natural form and as a combination with magnesium, potassium, and calcium than when given alone.⁴¹

Magnesium is also an essential cofactor for the delta-6-desaturase enzyme, which is the rate-limiting step for the conversion of linoleic acid (LA) to gamma-LA (GLA).^{42–44} GLA, in turn, elongates to form DGLA (dihomo-gamma-linoleic acid), the precursor for prostaglandin E₁ (PGE₁), is both a vasodilator and platelet inhibitor.^{42–44} Low magnesium states lead to insufficient amounts of PGE₁, causing vasoconstriction and increased BP.^{42–44}

In addition to BP, magnesium regulates intracellular calcium, sodium, potassium, and pH as well as left ventricular mass, insulin sensitivity, and arterial compliance.^{17,20} Magnesium also suppresses circulating Na⁺K⁺ATPase inhibitory activity that reduces vascular tone.²⁴

The calcium channel blocker mimetic effect of magnesium results in production of vasodilator prostacyclins and nitric oxide and alters the vascular responses to vasoactive agonists.⁴⁴ These varied biochemical reactions control vascular contraction and dilation, growth and apoptosis, differentiation, and inflammation.⁴⁴ Alterations in magnesium transport systems may predispose patients to hypertension and subsequent cardio-

vascular disease.^{45–48} Magnesium efflux and influx transport systems have been well characterized in humans. Magnesium efflux occurs via Na⁺-dependent and Na⁺-independent pathways. Magnesium influx is controlled by Mrs2p, SLC41A1, ACDP2, Mag T1, TRPM6, and TRPM7 (melastatin).^{45–48} In particular, increased Mg⁺⁺ efflux through altered regulation of the vascular Na⁺/Mg⁺⁺ exchanger, and decreased Mg influx due to defective vascular and renal TRPM6/7 expression/activity may be important.^{45–48} TRPM6 is found primarily in epithelial cells. TRPM7 is ubiquitously expressed and is implicated as a signaling kinase involved in vascular smooth muscle cell growth, apoptosis, adhesion, contraction, cytoskeletal organization and migration, and is modulated by vasoactive agents, pressure, stretch, and osmotic changes.⁴⁸ TRPM7 thus alters intracellular magnesium levels through changes in efflux and influx, which may be related to the onset and perpetuation of hypertension.⁴⁸

Research involving new imaging techniques to measure intracellular magnesium, such as P-nuclear magnetic resonance and magnesium-specific ion-selective electrodes, which measure intracellular and extracellular free concentrations of magnesium, and fluorescent probes will further enhance our understanding of the role of magnesium in hypertension.^{17,49} Intracellular magnesium such as red blood cell magnesium is a more accurate reflection of total body magnesium stores.

THE “IONIC HYPOTHESIS” OF RESNICK AND THE ROLE OF MAGNESIUM AND OTHER IONS

The ionic hypothesis of hypertension and other metabolic disorders by Resnick⁵⁰ is characterized by the following: (1) increased intracellular free calcium and reduced intracellular free magnesium determine the amount of vasoconstriction or vasodilation; (2) an elevated glucose and low-density lipoprotein cholesterol increase the intracellular calcium and/or lower intracellular magnesium in vascular smooth muscle cells; (3) hypertension, insulin resistance, and type II diabetes mellitus are associated with an increased intracellular calcium and decreased intracellular magnesium, which all respond to weight loss; (4) weight loss also decreases intracellular calcium levels; (5) dietary calcium suppressible hormones such as parathyroid hormone (PTH) and 1,25 vitamin D are vasoactive and promote calcium uptake in vascular smooth muscle cells and cardiac muscle; (6) the higher the PTH concentration, the greater the fall in BP, and the greater the reduction in PTH and 1,25 vitamin D, the greater the BP reduction; (7) individuals with salt-sensitive and calcium-sensitive hypertension have elevated intracellular calcium PTH and 1,25 vitamin D, but low intracellular magnesium; (8) dietary calcium reverses abnormal calcium indices and lowers BP; (9) dietary potassium reduces urinary calcium excretion and 1,25 vitamin D plasma levels; and (10) magnesium

intake reduces tissue calcium accumulation. Increased intake of magnesium, potassium, and calcium with concomitant reductions in sodium intake may lower BP more effectively than changing the intake of any single mineral.

CONCLUSIONS

The overall effect of diet on BP is determined by the net contribution of various nutrients on cytosolic-free minerals such as potassium, calcium magnesium, and sodium. Measurements of intracellular magnesium are more indicative of body stores and should be used in conjunction with serum magnesium and urinary magnesium to accurately determine magnesium deficiencies. Consumption of 500 mg to 1000 mg of magnesium may lower BP as much as 2.7 mm Hg to 5.6 mm Hg systolic and 1.7 mm Hg to 3.4 mm Hg diastolic as measured by causal office BP readings, home BP measurements, or 24-hour ambulatory BP monitoring. However, the variability in study design and methodology, doses and type of magnesium used, pretreatment magnesium and BP levels, population studied, concomitant sodium, potassium and calcium intake, and other issues make definitive conclusions about the magnitude of BP reduction difficult. Magnesium lowers intracellular sodium and calcium, which enhances BP reduction. Magnesium is a natural calcium channel blocker, blocks sodium attachment to vascular smooth muscle cells, increases vasodilating PGE, binds potassium in a cooperative manner, increases nitric oxide, improves endothelial dysfunction, causes vasodilation, and reduces BP. Some genetic defects in magnesium transport may be causative in hypertension. Combinations of magnesium and potassium with low-sodium intakes are more effective in reducing BP than using single minerals. It is recommended that 1000 mg of magnesium be combined with 4.7 g of potassium and <1.5 g of sodium per day through both diet and supplements to maximize BP reduction.²⁷ Combining magnesium with taurine has additive antihypertensive effects and lowers intracellular sodium and calcium. It is recommended that about 1000 mg to 2000 mg of taurine be added to this regimen. These can be administered separately or as magnesium taurate combinations, which are available from many reputable nutrition companies and variable doses of 100 mg to 500 mg of magnesium taurate. The use of chelated magnesium with an amino acid is better absorbed and reduces diarrhea. Taurine has a mild diuretic effect, but is otherwise well tolerated without adverse effects. Magnesium should be avoided or used with caution in any patient with renal impairment or patients with neuromuscular disorders. Magnesium has additive antihypertensive effects with all antihypertensive drugs and should thus be routinely administered unless patients have specific contraindications such as renal insufficiency or they are taking medications that could result in magnesium retention. The role of magnesium supplementation in

the prevention or treatment of CVD, CHD, CVA, cardiac arrhythmias, insulin resistance, hyperglycemia, diabetes mellitus, left ventricular hypertrophy, and dyslipidemia will require more definitive clinical trials in the future.

RECOMMENDATIONS

Americans consume 3 to 4 times the sodium and about one third the magnesium and potassium that is recommended by current guidelines. A high intake of potassium, magnesium, and possibly calcium through increased consumption of fruits and vegetables, the DASH diet and supplements, and reduced intake of sodium are important for the prevention of hypertension and major public health problems such as CVD, CHD, and stroke.

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