The Effect of Magnesium Supplementation on Blood Pressure: A Meta-Analysis of Randomized Clinical Trials

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Background: An increased intake of magnesium might lower blood pressure (BP), yet evidence from clinical trials is inconsistent, perhaps as a result of small sample size or heterogeneity in study design.

Methods: We performed a meta-analysis of randomized trials that tested the effects of magnesium supplementation on BP. Twenty trials meeting the inclusion criteria were identified. Random effects models and meta-regression methods were used to pool study results and to determine the dose–response relationship of magnesium to BP.

Results: The 20 studies included 14 of hypertensive and 6 of normotensive persons totaling 1220 participants. The doses of magnesium ranged from 10 to 40 mmol/day (median, 15.4 mmol/day). Magnesium supplementation resulted in only a small overall reduction in BP. The pooled net estimates of BP change (95% confidence interval [CI]) were −0.6 (−2.2 to 1.0) mm Hg for systolic BP and −0.8 (−1.9 to 0.4) mm Hg for diastolic BP. However, there was an apparent dose-dependent effect of magnesium, with reductions of 4.3 mm Hg systolic BP (95% CI 6.3 to 2.2; $P < .001$) and of 2.3 mm Hg diastolic BP (95% CI 4.9 to 0.0; $P = .09$) for each 10 mmol/day increase in magnesium dose.

Conclusions: Our meta-analysis detected dose-dependent BP reductions from magnesium supplementation. However, adequately powered trials with sufficiently high doses of magnesium supplements need to be performed to confirm this relationship. Am J Hypertens 2002;15: 691–696 © 2002 American Journal of Hypertension, Ltd.

Key Words: Meta-analysis, magnesium supplements, blood pressure.

Experimental and metabolic studies suggest that magnesium has a role in blood pressure (BP) regulation.[1] For example, in vitro studies have shown that magnesium influences cell membrane sodium pump activity, which in turn affects sodium–potassium transport across cell membranes, and subsequently vascular tone and reactivity.[2] In addition, clinical studies have demonstrated significant BP reductions with parenteral high-dose magnesium in patients with eclampsia and glomerulonephritis.[3,4] This line of evidence, albeit indirect, suggests that an increased intake of magnesium might lower BP in otherwise healthy populations of free-living individuals.

In observational epidemiologic studies, several studies suggest an inverse association between dietary magnesium intake and BP.[5] However, this association is difficult to interpret because of the imprecision of dietary data and colinearity of magnesium intake with other dietary components.[6] In 1983, Dyckner and Wester[7] reported results from the first clinical trial of low-dose magnesium supplementation. Since then, a large number of supplement trials in humans have been published.[8–32] Results of these trials have been inconsistent, perhaps because of small sample sizes or design limitations. The process of conducting a meta-analysis allows one to explore the basis of this heterogeneity and to estimate an effect size with precision.[33–36]

The objective of this meta-analysis was to determine whether magnesium supplementation reduces BP, to identify the dose–response relationship, and to determine trial characteristics associated with greatest BP reductions.

Received December 26, 2001. First decision March 13, 2002. Accepted March 26, 2002.

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This study was supported by a research fellowship grant from the Four Schools Physician–Scientist Program (VKS), grants from the NIH NIDDK (MJK) K24 DK02856 and NHLBI K08 HL03857 (ERM).

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0895-7061/02/$22.00
PII S0895-7061(02)02964-3

Table 1. Participants and study design characteristics of 20 magnesium supplementation trials

Author, Year	No. of Subjects	Mean age (y)	% Female	Study Design	Duration (wk)	Pretreatment BP (mm Hg)		Mg Supplement	Mg Dose (mmol/day)	Diuretic Use
						SBP	DBP			
Dyckner et al, 1983	39	65	66	P -	24	153	92	Mg aspartate	15.0	Yes
Reyes et al, 1984	21	57	80	P D	3	158	110	$MgCl_2$	15.8	Yes
Cappuccio et al, 1985	17	52	47	C D	4	154	100	Mg aspartate	15.0	No
Henderson et al, 1986	40	62	50	P -	24	156	90	MgO	12.4	Yes
Saito et al, 1988	20	57	25	P D	4	134	80	MgO	24.7	Yes
Nowson et al, 1989	25	63	32	P D	8	153	91	Mg aspartate	10.0	No
Patki et al, 1990	37	50	78	C D	8	155	100	$MgCl_2$	20.0	No
Zemel et al, 1990	13	51	14	P D	12	143	90	Mg aspartate	40.0	No
Lind et al, 1991	71	61	46	P D	24	150	92	Mg lactate & Mg citrate	15.0	No
TOHP, 1992	461	43	68	P D	24	125	84	Mg diglycine	15.0	No
Ferrara et al, 1992	14	48	43	P D	24	157	95	Mg pidolate	15.0	No
Widman et al, 1993	17	50	12	C D	9	154	99	$Mg(OH)_2$	28.3	No
Plum et al, 1994	39	39	39	C D	8	150	97	Mg aspartate	15.0	No
Witteman et al, 1994	91	57	100	P D	24	146	89	Mg aspartate	20.0	No
Purvis et al, 1994	28	54	86	C -	24	142	80	$MgCl_2$	15.8	No
Sanjuliani et al, 1996	15	50	53	C D	3	159	107	MgO	24.7	No
Itoh et al, 1997	33	65	68	P D	4	126	76	$Mg(OH)_2$	18.9	No
Sacks et al, 1998	153	39	100	P D	16	116	74	Mg lactate	14.0	No
Kawano et al, 1998	60	58	43	C -	8	134	81	MgO	20.0	No
Doyle et al, 1999	26	23	100	C D	4	113	77	$Mg(OH)_2$	10.3	No

BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; Mg = magnesium.

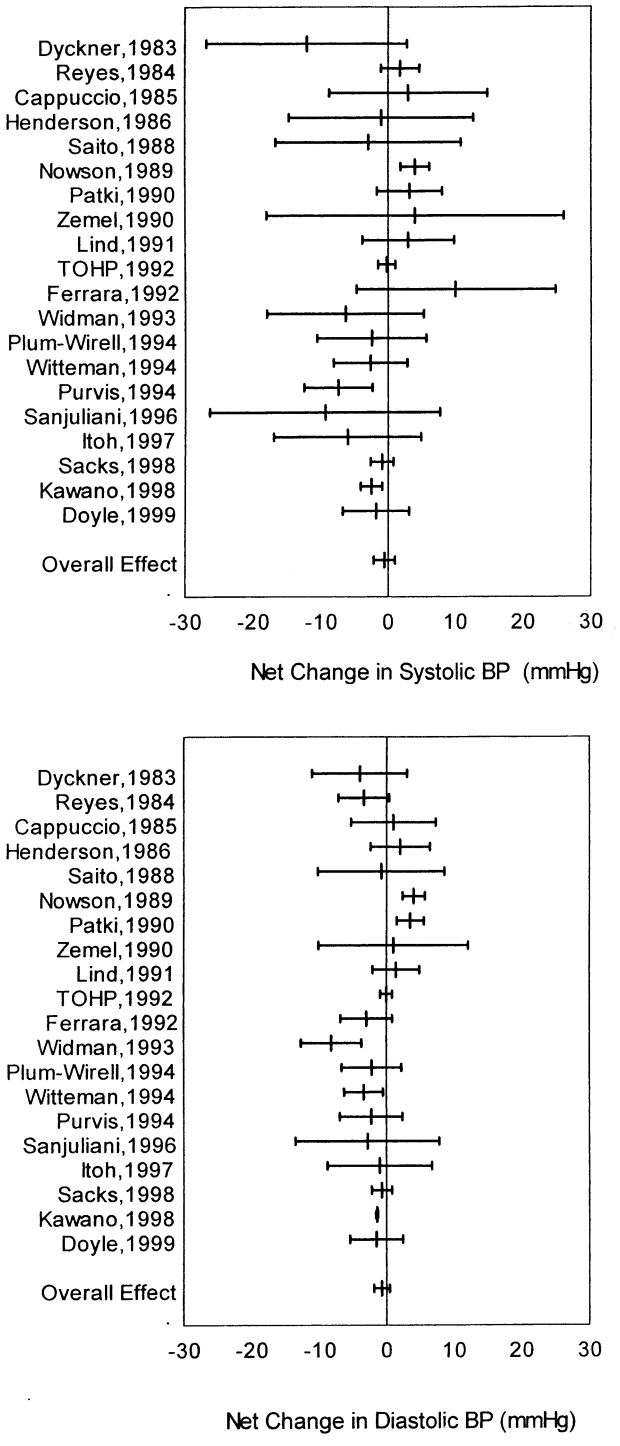

FIG. 1. Net change in systolic and diastolic blood pressure (BP) associated with magnesium (Mg) supplementation in 20 clinical trials. The overall effect is weighted by the inverse of the total variance of each trial.

Methods

We searched the English language literature for all reports on magnesium supplementation and BP in humans published before May 2001. Search strategies included: 1) a MEDLINE search using the medical subject headings magnesium and BP in clinical trials; 2) a review of reference lists from original research and review articles; and 3) a review of the authors' reference files. Thirty-one articles were identified.[2–33]

Our prespecified inclusion criteria were: 1) random allocation of participants, 2) use of magnesium supplementation alone as the active treatment, 3) presence of a control group, and 4) sufficient data to calculate the difference in BP change between the active treatment and control and the standard error of this difference. Twenty studies met the inclusion criteria. The major reasons for exclusion were: 1) nonrandomized treatment allocation,[2,30] 2) lack of a concurrent control group,[29] 3) insufficient data to calculate the net change in BP or standard error,[30–32] and 4) the combination of magnesium with other minerals that affect BP.[27,28,32]

Two investigators (SJ and VS) independently abstracted the articles. Disagreements or uncertainties were adjudicated by consensus. From each article, the following data were abstracted: 1) characteristics of the study population including sample size, age, gender, proportion with hypertension, baseline magnesium intake, and BP level, 2) characteristics of the design including duration of intervention, treatment dose, and type of magnesium carrier, and 3) change in BP and associated variance. For crossover trials, we used mean BP during the control period as the baseline values.

Statistical Analysis

For parallel trials, net change in BP was calculated as the mean difference (magnesium supplementation minus control) of the change (follow-up minus baseline) in BP. For crossover trials, net change was calculated as the mean difference between the end of the magnesium supplementation and control periods. To calculate the pooled effects, each study was assigned a weight equivalent to the reciprocal of the variance of net change. For parallel trials in which the variance of paired differences during the trial was reported separately for several groups, we calculated variance for net change using standard methods.[35]

Estimates of the mean effect of magnesium supplementation on BP and the corresponding 95% confidence intervals (CI) were calculated using both fixed effects and random effects models. Both approaches yielded similar patterns. Homogeneity of effect size across trials was tested by Q statistics.[34] Because there was substantial and significant heterogeneity in effect size across trials, we used meta-regression techniques to evaluate the impact of magnesium dose and other factors on study results.[35,36]

To examine potential publication bias, we plotted the sample sizes of the studies against their corresponding effect size.[35]

Results

Participant and design characteristics of the 20 clinical trials are presented in Table 1. The trials were conducted

Table 2. Meta-regression model of the efficacy magnesium supplementation on blood pressure reduction

Factor	SBP Difference Magnesium–Control		DBP Difference Magnesium–Control	
	Effect (95% CI)	*P*	Effect (95% CI)	*P*
Magnesium dose (per 10 mmol/day)	−4.3 (−6.3 to −2.2)	<.001	−2.3 (−4.9 to 0.0)	.09
Baseline BP (per 10 mm Hg)	0.8 (0.3 to 1.3)	.02	0.0 (−1.4 to 1.4)	.97
Intercept	2.7 (−9.7 to 15.1)	.67	−4.2 (−11.6 to 3.14)	.26

CI = confidence interval; other abbreviations as in Table 1.

between 1983 and 2001; the sample size varied from 13 to 461 participants, with a median of 30.5 participants per trial. The total number of participants was 1220. All of the trials were conducted in adults, with a range of mean ages from 23 to 65 years. Seventeen of the 20 trials included both men and women, whereas women were the sole participants in the remaining three trials. A crossover design was used in 8 trials, whereas a parallel arm design was used in the remaining 12 trials. Sixteen of the trials were double-blind, whereas the remaining 4 trials did not report information about blinding. The trials varied in length from 3 to 24 weeks, with a median duration of 8.5 weeks. The dose of magnesium supplementation in the active treatment group varied from 10 to 40 mmol/day, with a median of 15.4 mmol/day. Four trials were conducted in persons who were concurrently taking a diuretic. In the 20 trials, eight different compounds of magnesium were used (MgO, Mg aspartate, $MgCl_2$ $MgOH_2$, Mg diglyceride, Mg citrate, Mg lactate, and Mg pidolate).

Systolic BP (SBP) decreased in the magnesium group compared to the control in 14 of the 20 trials; in 2 trials, the SBP reduction was statistically significant, whereas in 1 trial, magnesium significantly increased SBP (Fig. 1). Overall, magnesium supplementation reduced SBP by 0.6 mm Hg (95% CI −2.2 to 1.0, $P = .051$). Diastolic BP (DBP) decreased in the magnesium group compared to control in 14 of the 20 trials. In three trials, the DBP reduction was statistically significant (Fig. 1). The pooled estimate of the effect of magnesium supplementation on DBP was a net decrease of 0.8 mm Hg (95% CI −2.1 to 0.5, $P = .142$). The test for heterogeneity was highly significant both for SBP and DBP changes ($P < .001$), indicating that additional factors could impact the efficacy of magnesium in reducing BP.

When limiting the analysis to the 16 double-blind studies (excluding single-blinded studies), a 10 mmol/day increase in magnesium intake was associated with a decrease in SBP of 3.4 mm Hg (95% CI 0.6 to 6.1, $P = .02$) and a decrease in DBP of 2.0 mm Hg (95% CI −0.9 to 5.0, $P = .18$). Limiting the analysis to the 14 hypertensive trials (i.e., trials with average baseline SBP >140 mm Hg or DBP >90 mm Hg), magnesium (per 10 mmol/day) decreased SBP by 3.3 mm Hg (95% CI −0.1 to 6.8, $P = .06$) and DBP by 2.3 mm Hg (95% CI −1.0 to 5.6, $P = .17$).

Table 2 summarizes the results of meta-regression analyses that examined the dose–response relationship between magnesium and BP (Fig. 2). For each 10 mmol/day larger dose of magnesium SBP decreased by 4.3 mm Hg (95% CI 6.3 to 2.2, $P < .001$) and DBP by 2.3 mm Hg (95% CI 4.9 to 0.0, $P = .09$). In addition, the effect of magnesium on SBP was stronger in trials with lower baseline SBP, although this effect was absent for DBP. The meta-regression model completely explained the residual heterogeneity for the effect of magnesium on SBP, but not on DBP (estimated between-study variation, $\tau = 2.3$ mm Hg). Other factors, including age, gender, trial design (crossover versus parallel), and duration were not significantly associated with magnesium efficacy.

The plot of sample size versus effect size was funnel-shaped with little variation in the average effect size for the studies with larger sample size (not shown), thus minimizing the possibility that our findings could be explained by publication bias.

Discussion

To our knowledge, this is the first quantitative review of randomized trials that tested the effect of magnesium supplementation on BP. Although magnesium supplementation resulted in a small overall reduction in BP, there was an apparent dose-dependent effect of magnesium, specifically reductions of 4.3 mm Hg SBP and of 2.3 mm Hg DBP for each 10 mmol/day increase in magnesium dose.

The majority of trials included in this study (>70%) showed reductions in either SBP or DBP individually, yet were likely underpowered to detect small reductions in BP. Larger effect sizes would be expected in hypertensive persons, but the paucity of large trials in persons with hypertension might explain why significant findings in individual studies for SBP reduction was found only in trials of normotensive persons.

Our results indicate a greater efficacy that magnesium supplementation may have at higher doses. Such findings might explain why small trials that administered small doses of magnesium (10 to 15 mmol/day) failed to detect significant effects. Few studies were conducted in the higher dose range of magnesium (20 to 40 mmol/day). Properly designed and adequately powered trials at higher dose ranges need to be performed to confirm the inverse dose–response relationship that we detected.

One potential limitation is a lack of data on dietary intake of magnesium. In those trials that enrolled partici-

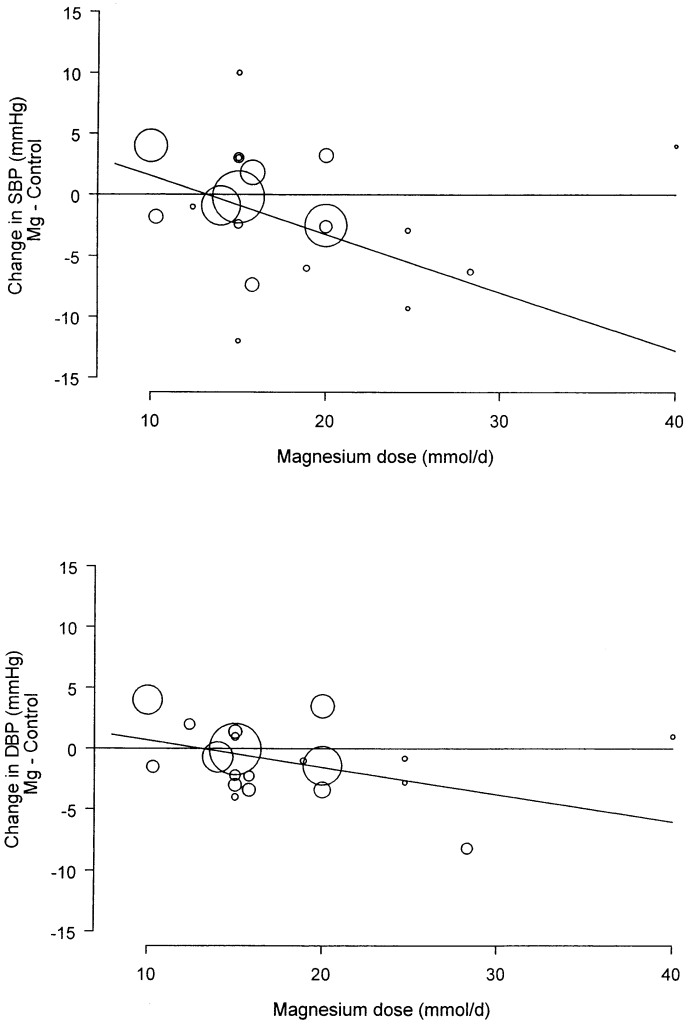

FIG. 2. Dose–response effect of Mg on systolic (SBP) and diastolic (DBP) blood pressure. Each **circle** represents a study, with the area of each **circle** inversely proportional to study variance. Other abbreviation as in Fig. 1.

pants diagnosed with hypertension, participants may have already increased dietary intake of magnesium-rich foods as a result of this diagnosis. Such modifications may have led to heterogeneity in the estimates of the magnesium–BP relationship. In addition, although the median amount of magnesium administered in these trials, 15 mmol/day, results in about a doubling of usual daily magnesium intake derived from diet (median ~12.5 mmol/day for men in the United States), it may not be a sufficiently large enough dose to produce a clinically relevant effect. Hence, as suggested by our pooled dose–response analysis, important BP-lowering effects may occur only at higher doses.

Other potential limitations include heterogeneity in study design, study participants, and in the type of magnesium supplement used. Absorption of magnesium supplements varies for different anions. Hence, some forms of administered magnesium may have had lower bioavailability, which would diminish the BP-lowering effect. Finally, our analysis contains only articles published in the English language. Studies in the English language literature may show a greater intervention effect than research that is never published or that is published in languages other than English. However, analysis of a funnel plot of study size did not show evidence of publication bias.

In summary, our meta-analysis detected significant, dose-dependent BP reductions from magnesium supplementation. This effect is consistent with experimental studies and with the effect of intravenous magnesium. However, there is still considerable uncertainty on the clinical utility of magnesium supplements. Adequately powered trials with sufficiently high doses of magnesium supplements need to be performed to confirm the inverse dose–response relationship observed in our study.

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