Effects of Magnesium Supplementation on Blood Pressure
A Meta-Analysis of Randomized Double-Blind Placebo-Controlled Trials

Xi Zhang,* Yufeng Li,* Liana C. Del Gobbo, Andrea Rosanoff, Jiawei Wang, Wen Zhang, Yiqing Song

Abstract—The antihypertensive effect of magnesium (Mg) supplementation remains controversial. We aimed to quantify the effect of oral Mg supplementation on blood pressure (BP) by synthesizing available evidence from randomized, double-blind, placebo-controlled trials. We searched trials of Mg supplementation on normotensive and hypertensive adults published up to February 1, 2016 from MEDLINE and EMBASE databases; 34 trials involving 2028 participants were eligible for this meta-analysis. Weighted mean differences of changes in BP and serum Mg were calculated by random-effects meta-analysis. Mg supplementation at a median dose of 368 mg/d for a median duration of 3 months significantly reduced systolic BP by 2.00 mm Hg (95% confidence interval, 0.43–3.58) and diastolic BP by 1.78 mm Hg (95% confidence interval, 0.73–2.82); these reductions were accompanied by 0.05 mmol/L (95% confidence interval, 0.03, 0.07) elevation of serum Mg compared with placebo. Using a restricted cubic spline curve, we found that Mg supplementation with a dose of 300 mg/d or duration of 1 month is sufficient to elevate serum Mg and reduce BP; and serum Mg was negatively associated with diastolic BP but not systolic BP (all $P<0.05$). In the stratified analyses, a greater reduction in BP tended to be found in trials with high quality or low dropout rate (all P values for interaction <0.05). However, residual heterogeneity may still exist after considering these possible factors. Our findings indicate a causal effect of Mg supplementation on lowering BPs in adults. Further well-designed trials are warranted to validate the BP-lowering efficacy of optimal Mg treatment. **(*Hypertension*. 2016;68:324-333. DOI: 10.1161/HYPERTENSIONAHA.116.07664.)** ● **Online Data Supplement**

Key Words: blood pressure ■ hypertension ■ magnesium ■ meta-analysis ■ randomized controlled trial

Magnesium (Mg), an essential element in the human body, may have beneficial health effects for the primary prevention of hypertension. Given the increasing prevalence and incidence of hypertension, the identification of effective and safe preventive measures that offer even modest blood pressure (BP)–lowering effects could have a significant public health impact. Several lines of evidence from laboratory research have suggested some underlying mechanisms. Mg may play a critical role in BP regulation, through directly stimulating prostacyclin and nitric oxide formation,[1] modulating endothelium-dependent and endothelium-independent vasodilation,[2,3] reducing vascular tone and reactivity,[4] and preventing vascular injury via its antioxidant and anti-inflammatory functions.[5,6] Numerous experimental studies have implicated a pathophysiological link between lower Mg content in the blood (hypomagnesemia) or tissue[7–9] and hypertension in various animal models.

There is long-standing interest in the promising yet unproven role of Mg in the regulation of BP for the prevention of hypertension, although evidence from human studies has been both inconsistent and controversial. Observational epidemiological evidence also suggested a negative association between dietary Mg intake and BP[10]; however, effects of Mg on both systolic and diastolic BPs were not consistent among individual trials of Mg supplementation.[11] Previous systematic reviews and meta-analyses based on randomized trials have also been less conclusive for both systolic and diastolic BPs.[11–13] For instance, a recent meta-analysis reviewed 23 trials with a total of 1173 participants and reported a significant decrease in systolic BP of 2 to 3 mm Hg and diastolic BP of 3 to 4 mm Hg elicited by a median dose of 410 mg/d Mg supplementation for an average of 11 weeks.[14] Nevertheless, there was considerable heterogeneity across trials in terms of trial quality, sample sizes, and participant characteristics. In particular, whether trial quality, treatment compliance, or participants' baseline Mg status would modify the effects of Mg on lowering BPs remained unexplored in all previous studies, possibly because of the limited number of suitable trials,

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From the Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University (X.Z., Y.S.); Department of Endocrinology, Beijing Pinggu Hospital, Beijing, China (Y.L.); Department of Medicine, Division of Cardiovascular Medicine, Stanford University, CA (L.C.D.G.); Center for Magnesium Education and Research, Pahoa, HI (A.R.); Douglas Mental Health University Institute, McGill University, Montreal, Quebec, Canada (J.W.); and Department of Epidemiology, School of Medicine, Fukushima Medical University, Fukushima, Japan (W.Z.).

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*These authors contributed equally to this work.

Correspondence to Yiqing Song, Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, 1050 Wishard Blvd, RG 5116, Indianapolis, IN 46202. E-mail yiqsong@iu.edu

especially well-designed and conducted randomized controlled trials (RCTs).

To reliably test the BP-lowering effects of oral Mg supplementation, we conducted a comprehensive meta-analysis to synthesize only direct evidence from randomized, double-blind, placebo-controlled trials. To evaluate the robustness of the overall results, we also examined whether and to what extent changes in BP were related to elevation in serum Mg levels elicited by Mg supplementation.

Methods

Search Strategy

We electronically searched and identified all relevant articles evaluating the antihypertensive effect of Mg based on RCTs of Mg supplementation from the MEDLINE and EMBASE databases published up to February 1, 2016. We separately searched magnesium or Mg for Mg, hypertension or blood pressure for BP, supplementation, supplement, intervention, randomized controlled trial, randomized clinical trial, randomized trial, controlled trial, or clinical trial for RCTs in article texts or Medical Subject Headings terms and then combined these 3 search results using the Boolean logic operator AND. All searches were limited to English language and human adults. Additionally, all bibliographies of related articles and current review articles were manually screened for additional potentially relevant articles.

Selection Criteria

We included RCTs that assessed the response of BPs to Mg supplementation. To minimize potential bias and confounding, we focused solely on RCTs of oral Mg supplementation. Exclusion criteria were as follows: (1) studies including pregnant or lactating women; (2) studies including patients with malignancy, severe infectious disease, active liver or renal disease, or other severe illnesses; (3) supplements combined with other minerals that affect BP and duration of Mg supplementation ≤1 week; and (4) nonrandom, open-label, or self-controlled trials. Trials with combined supplements were eligible only when the combined antihypertensive drugs or minerals were applied identically in control and treatment groups.

Study Selection

Title and abstract screening was performed for each article to remove obviously irrelevant and duplicated reports. Articles deemed potentially eligible by title and abstract screening were re-examined by full-text review according to the above standard inclusion and exclusion criteria. The eligibility of articles was finally determined by 2 independent authors (X.Z. and Y.L.). Any discrepancies were resolved through discussion.

Data Extraction

Two researchers (X.Z. and A.R.) independently extracted available data and relevant information into a standard form, which included general information on the publication (first author's last name and first initial, year of publication, and study location), participants (sex proportion, mean age or age range, number of participants, comorbidities, and combination therapy), study design (follow-up years, Mg formulation, and dosage), and serum Mg and BP measures at baseline and after treatment. If repeated measures of Mg levels and BP at several time points were reported in a single trial, the last measures were selected for overall analysis; they were both included in the subgroup analysis only if they were stratified into different separate subgroups. The accuracy of extracted data was double checked by another researcher (Y.L.).

Quality of Trials

We applied the Agency for Healthcare Research and Quality criteria for quality assessment of RCTs to evaluate the risk of bias in all identified trials.[15,16] These criteria assessed adequate sequence generation for randomization, allocation concealment, blinding of outcomes assessors, similarity of groups at baseline, selective reporting, incomplete outcome data, and description of losses and exclusions by 3 different degrees for risk of bias (high, low, or unclear). We also assessed overall trial quality according to the 5-point Jadad score of randomization, double blinding, and withdrawals and dropouts. Points were awarded from 0 to 5. We sorted all trials into high-quality (>3) and low-quality (≤3) groups, which were used for subgroup analysis stratified by trail quality.

Statistical Methods

To evaluate the overall effects of Mg supplementation on BP, we compared the mean changes of systolic and diastolic BP between treatment and placebo groups after treatment by calculating weighted mean differences and 95% confidence intervals (CIs) using a random-effects meta-analysis model.[17] We also estimated weighted mean differences for serum Mg concentrations to assess the effectiveness of Mg supplementation on Mg status. We assessed the between-study heterogeneity by calculating both τ statistic and I^2 statistics. The percentages of I^2 around 25% (I^2=25), 50% (I^2=50), and 75% (I^2=75) indicate low, medium, and high heterogeneity, respectively. Tau, τ, is the estimate of between-study SD that indicates the extent to which such heterogeneity affects the final meta-analysis results.

To explore major sources of heterogeneity and assess the robustness of the overall meta-analysis results, we conducted subgroup analyses stratified by predefined subgroups, including age (<65 or ≥ 65 years), sex (trials with women ≥50% or men >50%), study location (America, Asia, Europe, or Latin America), Mg formulation (organic: Mg lactate, Mg citrate, Mg pidolate, and Mg aspartate or inorganic: MgO, $MgCl_2$, or $Mg(OH)_2$), elemental Mg dosage in mg (<300, 300–399, or ≥400 mg/d), duration of trials (<30, 30–89, or ≥90 d), baseline Mg (quartiles categories of baseline serum Mg), baseline BP status (hypertensive or normotensive), medication use history (taking antihypertensive or diabetic drugs or off medication), methods of BP measures (sphygmomanometer or automatic monitor), and crossover design (yes or no). Furthermore, to assess whether trial quality contributed to between-study heterogeneity, we performed subgroup analyses stratified by quality assessment of RCTs, including overall trial quality (high versus low), sample size (<50 versus ≥50), dropout rate (<10% versus ≥10%), and success of randomization. Success of randomization was assessed by examining the comparability of basal serum Mg and BPs between the randomly assigned Mg group and the placebo group in individual trials or according to the description of randomization in the individual article. Publication bias was evaluated first by visual inspection of the funnel plots and then by Begg adjusted rank correlation test.[18]

A restricted cubic spline regression analysis was performed to assess possible dose and time responses of BPs and serum Mg to Mg supplementation. For systolic or diastolic BP or serum Mg, we calculated restricted cubic spline with 3 fixed knots at 10%, 50%, and 90% percentiles through the overall distributions based on all included studies for each eligible trial, separately, and then combined them to depict possible dose- and time-dependent relations of BPs and serum Mg levels to Mg supplementation.[19,20]

Stata (version 14; StataCorp, College Station, TX) software was used for all statistical analyses. A 2-tailed P<0.05 was considered statistically significant.

Results

Our electronic and manual search identified a total of 615 potentially relevant publications. After excluding duplicative and irrelevant publications by screening titles and abstracts and reviewing the full texts, 34 RCTs from 34 published articles met our inclusion criteria (Figure S1 in the online-only Data Supplement).

Characteristics of Included Trials and Participants

We identified 34 eligible randomized double-blind placebo-controlled trials that included a total of 2028 normotensive or hypertensive participants (range: 13–461), aged between 18

and 84 years, with 1010 participants receiving Mg supplementation and 1018 placebo (Table). Among them, 27 studies also measured serum Mg.

Eleven trials used a crossover study design, and others were parallel designed; 55% (908) of the study population were women, and 45% (751) were men. The studies were conducted in America (4 trials), Asia (3 trials), Europe (17 trials), and Latin America (9 trials). Most of the participants were either clearly hypertensive or normotensive (16 and 18 trials, respectively), and only 1 trial included participants with borderline hypertension.[21] Most of the trials required that hypertensive patients go off medications ≥1 month (22 of 34 trials); and patients in 4 trials were still taking medications during the trials.[22–25] Additionally, 2 trials included participants with low serum Mg (<0.74 mmol/L).[25,26] BPs were generally measured by sphygmomanometer (14 trials) or automatic monitor (9 trials), and only 2 trials applied ambulatory monitor recording of 24-hour BPs.[27,28]

The trial durations varied from 3 weeks to 6 months, although the vast majority (30 of 33 trials) were longer than 1 month. Mg supplements differed between studies in formulation and dosage. A total of 7 types of organic (15 trials) and inorganic Mg (18 trials) supplements were used: MgO, $Mg(OH)_2$, $MgCl_2$, Mg aspartate, Mg lactate, Mg citrate, and Mg pidolate. The daily dosage of Mg supplements in elemental Mg ranged from 240 to 960 mg, most of which (28 trials, 82%) were equal or higher than the levels of US Recommended Dietary Allowance for adults (310–320 mg/d for women and 400–420 mg/d for men[29]). The characteristics of all identified trials are presented in Table S1.

Effects on Lowering BPs and Elevating Serum Mg

Compared with the placebo groups of 34 trials, Mg supplementation at a median dose of 368 mg/d (range: 238–960 mg/d) for a median duration of 3 months (range: 3 weeks to 6 months) led to overall reductions in systolic BP (weighted mean difference=2.00 mm Hg; 95% CI, 0.43–3.58; P=0.01; τ=3.1; I^2=61.8; Figure 1) and diastolic BP (1.78 mm Hg; 95% CI, 0.73–2.82; P=0.001; τ=2.2; I^2=63.8; Figure 2), while concomitantly elevating serum Mg levels by 0.05 mmol/L (95% CI, 0.03–0.07; P<0.001; τ=0.03; I^2=86.2) among 27 trials (Figure S2). Begger tests did not reveal substantial publication bias for the overall effects of Mg on systolic BP, diastolic BP, or serum Mg (P_{Begger}>0.05).

Sources of Between-Study Heterogeneity by Subgroup Analyses

As shown in Table, nonsignificant differences in Mg effects on BPs were found by subgroup analyses stratified by age; sex; study location; hypertensive status; baseline Mg status; antihypertensive or diabetic medication use history; method, times, and position for BP measures; study design; Mg formulation; dosage; and trial duration (all P values for interaction >0.05). Systolic and diastolic BPs were significantly decreased by 5.69 mm Hg (95% CI, 1.00–10.37; τ=4.5; I^2=54.3) and 2.55 mm Hg (95% CI, 0.19–4.92; τ=1.9; I^2=37.0), respectively, among participants taking antihypertensive or antidiabetic drugs (n=7 trials), whereas reduction in BPs was nonsignificant among participants off antihypertensive or antidiabetic medications (systolic BP: −0.13 mm Hg; 95% CI, −4.25 to 4.00; τ=5.6; I^2=73.1 and diastolic BP: 1.52 mm Hg; 95% CI, −1.09 to 4.12; τ=3.7; I^2=80.5; n=11 trials). However, P value for interaction was >0.05. The overall effects of Mg on serum Mg varied depending on the study location, Mg formulation, and baseline Mg status (all P values for interaction ≤0.01).

Additionally, in the sensitivity analysis, inclusion or exclusion of any individual trial did not substantially change the overall results for BPs and serum Mg.

Dose and Time Responses of BPs to Mg Supplementation

Our dose- and time-response analyses of data from 27 trials showed that oral Mg supplementations at a dose of 200 mg/d or with a duration of 1 month was sufficient to significantly raise serum Mg (all P values <0.001). Higher doses (≥300 mg/d) or longer durations (≥2 months) were required to achieve maximal levels of serum Mg by Mg supplementation (Figures 3A and 4A). Consistently, there was a significant reduction in systolic BP accompanying rises in serum Mg levels in a similar nonlinear time- and dose-dependent manner (both P linearity=0.07; n=34 trials; Figures 3B and 4B), whereas dose- and time-dependent reduction in diastolic BP seemed to be linear (all P linearity=0.02; Figures 3C and 4C). Furthermore, a positive relation between serum Mg elevation and the degree of diastolic BP lowering was found, and neither the linear nor curvilinear dose- and time-dependent relationship was significant for systolic BP. On average, each 0.1 mmol/L increment in serum Mg was associated with a reduction of 2.26 mm Hg (95% CI, 0.27–4.26; n=20 trials) in diastolic BP (Figure 5).

Quality Assessment of Included Trials

Trial quality may have an impact on the overall results of systolic and diastolic BPs (Table). However, the process of randomization was insufficiently described in identified studies, ie, only 30% seemed to have adequate sequence generation and 15% had low risk of bias in allocation concealment (Figure S3). Of the 24 high-quality trials, both systolic and diastolic BPs were significantly decreased by Mg treatment (systolic BP: −3.37 mm Hg; 95% CI, −5.34 to −1.40 and diastolic BP: −2.50 mm Hg; 95% CI, −3.65 to −1.36). In contrast, changes in systolic and diastolic BP were nonsignificant in the data from the 10 low-quality trials (systolic BP: 0.83 mm Hg; 95% CI, −0.89 to 2.56 and diastolic BP: 0.35 mm Hg; 95% CI, −1.45 to 2.15). The interactions were statistically significant between trials with high quality and trials with low quality for both systolic and diastolic BPs (P values for interaction <0.05). Also, greater reductions in BPs tended to be observed among trials with low dropout rate (≥10% versus <10%; P for interaction <0.05 for both systolic and diastolic BPs).

Discussion

In this meta-analysis of 34 randomized double-blind placebo-controlled trials involving a total of 2028 participants, we found that oral Mg supplementation led to a significant reduction in both systolic and diastolic BPs (2.00 and 1.78 mm Hg, respectively), although systolic BP and diastolic BP responses differed slightly in dose- and duration-dependent manners, respectively.

Table. Stratified Meta-Analysis of Mg Supplementation on Serum Mg, SBP, and DBP From RCT Data

Subgroups	Serum Mg, mmol/L				SBP, mm Hg				DBP, mm Hg		
	No of Studies*	WMD (95% CI)	τ/I²	P†	No of Studies*	WMD (95% CI)	τ/I²	P†	WMD (95% CI)	τ/I²	P†
Total	27 (822/800)	0.05 (0.03 to 0.07)	0.03/86.2		34 (1010/1018)	−2.00 (−3.58 to −0.43)	3.1/61.8		−1.78 (−2.82 to −0.73)	2.2/63.8	
Demographic											
Age, y				0.92				0.52			0.15
<65	15 (490/495)	0.05 (0.02 to 0.08)	0.05/90.1		18 (612/674)	−1.55 (−3.42 to 0.33)	2.6/60.9		−1.17 (−2.61 to 0.27)	2.4/73.3	
≥65	12 (332/305)	0.05 (0.03 to 0.07)	0.03/76.1		16 (398/343)	−2.61 (−5.62 to 0.40)	4.4/63.3		−2.97 (−4.05 to −1.88)	0.0/0.0	
Sex				0.15				0.86			0.88
Women (≥50%)	16 (404/374)	0.07 (0.04 to 0.09)	0.05/88.1		21 (521/518)	−2.10 (−4.35 to 0.14)	3.1/61.1		−1.95 (−3.49 to 0.41)	2.9/69.9	
Men (>50%)	11 (418/426)	0.03 (0.006 to 0.05)	0.03/81.0		13 (489/499)	−1.82 (−4.29 to 0.66)	3.6/63.7		−1.84 (−3.44 to −0.24)	1.6/49.2	
Study location				0.004				0.52			0.10
America	2 (180/184)	0.02 (−0.01 to 0.06)	0.02/57.6		4 (275/336)	−1.45 (−3.93 to 1.03)	1.8/68.4		−0.29 (−1.05 to 0.47)	0.0/0.0	
Asia	3 (117/108)	0.02 (−0.01 to 0.05)	0.02/44.7		3 (117/108)	0.19 (−5.10 to 5.49)	3.5/60.2		1.09 (−3.21 to 5.40)	3.2/77.7	
Europe	13 (282/270)	0.02 (−0.002 to 0.04)	0.03/74.1		17 (360/322)	−2.28 (−5.21 to 0.66)	4.7/68.1		−2.54 (−4.87 to −0.20)	2.0/51.4	
Latin America	8 (235/229)	0.12 (0.08 to 0.16)	0.05/81.3		9 (243/236)	−2.89 (−6.30 to 0.51)	3.3/45.1		−2.52 (−3.89 to −1.14)	2.1/38.0	
Mg supplementation											
Formulation				0.01				0.12			0.31
Inorganic	14 (428/411)	0.08 (0.04 to 0.12)	0.07/88.8		18 (456/440)	−3.52 (−5.75 to −1.29)	3.1/49.7		−2.39 (−4.34 to −0.43)	3.3/72.0	
Organic	12 (221/211)	0.02 (0.004 to 0.04)	0.02/78.6		15 (327/344)	−0.38 (−3.00 to 2.23)	3.5/61.3		−1.32 (−2.54 to −0.11)	1.3/34.7	
Dosage, mg/d				0.46				0.72			0.62
<300	3 (64/62)	−0.004 (−0.04 to 0.04)	0.0/0.0		3 (64/62)	−5.33 (−7.92 to −2.74)	0.0/0.0		−3.34 (−6.74 to 0.05)	2.2/54.0	
300–399	16 (520/520)	0.06 (0.03 to 0.08)	0.05/89.9		20 (680/709)	−1.31 (−3.23 to 0.60)	2.8/62.3		−1.47 (−2.54 to −0.40)	1.4/46.6	
≥400	8 (232/211)	0.06 (0.03 to 0.09)	0.04/78.9		11 (266/246)	−2.37 (−5.95 to 1.21)	4.2/55.3		−1.67 (−4.41 to 1.08)	3.7/75.0	
Duration, d				0.27				0.87			0.43
<30	4 (52/39)	0.05 (0.04 to 0.06)	0.0/0.0		8 (128/114)	−0.19 (−2.84 to 2.45)	1.5/14.4		−0.23 (−2.92 to 2.46)	2.8/66.1	
30–89	12 (283/282)	0.03 (−0.004 to 0.06)	0.05/87.3		16 (360/332)	−2.82 (−5.43 to −0.22)	4.1/68.7		−1.74 (−3.46 to −0.01)	2.9/73.8	
≥90	13 (494/486)	0.07 (0.05 to 0.10)	0.04/84.7		15 (645/666)	−0.76 (−2.77 to 1.24)	2.2/50.1		−1.67 (−3.00 to 0.34)	1.6/54.0	
Baseline Mg, mmol/L				0.005				0.21			0.90
Q1 (<0.71)	6 (206/200)	0.15 (0.11 to 0.18)	0.03/62.0		6 (206/200)	−4.50 (−7.24 to −1.76)	0.0/0.0		−5.05 (−9.12 to −0.97)	0.0/0.0	
Q2 (0.72–0.82)	7 (139/137)	0.02 (−0.02 to 0.05)	0.02/45.0		7 (139/137)	1.04 (−1.55 to 3.62)	0.0/0.0		−0.28 (−5.65 to 5.08)	0.0/0.0	
Q3 (0.83–0.88)	5 (143/124)	0.03 (0.02 to 0.04)	0.01/30.0		6 (143/124)	−0.96 (−5.31 to 3.40)	0.0/0.0		−0.80 (−5.10 to 3.50)	3.9/69.7	
Q4 (≥0.88)	7 (355/360)	0.02 (−0.001 to 0.04)	0.03/63.9		6 (355/360)	−3.70 (−5.47 to 1.94)	0.0/0.0		−1.92 (−4.82 to 0.98)	0.0/0.0	

(*Continued*)

Table. Continued

Subgroups	Serum Mg, mmol/L				SBP, mm Hg				DBP, mm Hg		
	No of Studies*	WMD (95% CI)	τ/ℓ	*P*†	No of Studies*	WMD (95% CI)	τ/ℓ	*P*†	WMD (95% CI)	τ/ℓ	*P*†
Design factors											
Prior BP status				0.26				0.79			0.59
Normotensive	15 (569/557)	0.06 (0.03 to 0.10)	0.05/90.0		18 (703/746)	−1.78 (−3.33 to −0.23)	1.9/47.2		−1.43 (−2.52 to −0.35)	1.3/40.6	
Hypertensive	12 (247/236)	0.03 (0.02 to 0.05)	0.02/76.8		16 (307/271)	−2.16 (−5.71 to 1.40)	5.7/70.5		−2.11 (−4.17 to −0.05)	3.4/75.2	
Medication history‡				0.78				0.11			0.72
Yes	5 (127/122)	0.06 (0.03 to 0.10)	0.04/71.2		7 (136/131)	−5.69 (−10.4 to −1.00)	4.5/54.3		−2.55 (−4.92 to −0.19)	1.9/37.0	
No	10 (202/196)	0.05 (0.02 to 0.07)	0.04/90.0		11 (240/208)	0.13 (−4.00 to 4.25)	5.6/73.1		−1.52 (−4.12 to 1.09)	3.7/80.5	
BP measurements				0.26				0.58			0.74
Sphygmomanometer	11 (446/439)	0.04 (0.02 to 0.06)	0.02/82.9		14 (563/532)	−0.60 (−2.52 to 1.33)	2.1/43.8		−1.69 (−3.28 to −0.01)	2.2/69.1	
Automatic monitors	6 (161/151)	0.02 (−0.01 to 0.05)	0.02/56.2		9 (217/260)	−1.56 (−4.94 to 1.83)	3.9/72.0		−1.21 (−3.16 to 0.74)	2.1/62.4	
No of BP measure				0.71				0.44			0.25
2 times	4 (111/115)	0.01 (−0.03 to 0.06)	0.03/78.5		5 (161/139)	−1.78 (−6.63 to 3.08)	3.9/53.7		1.17 (−1.51 to 3.84)	1.0/17.8	
3 times	5 (257/246)	0.04 (0.03 to 0.06)	0.01/47.2		7 (307/311)	−0.71 (−3.28 to 1.87)	2.2/51.0		−2.04 (−4.17 to 0.09)	2.0/61.8	
5 times	2 (16/15)	0.02 (−0.04 to 0.08)	0.04/90.6		3 (23/23)	0.89 (−8.09 to 9.86)	6.0/57.1		−1.80 (−3.76 to 0.17)	0.0/0.0	
Position of BP measure				0.51				0.57			0.57
Sitting	8 (467/470)	0.08 (0.05 to 0.11)	0.06/90.8		11 (554/559)	−3.44 (−5.69 to −1.20)	2.6/59.3		−3.03 (−2.69 to −0.60)	2.3/66.5	
Supine	11 (166/148)	0.02 (−0.002 to 0.05)	0.04/80.0		13 (208/163)	0.79 (−3.15 to 4.72)	5.7/68.1		−0.03 (−1.85 to 1.79)	2.2/55.3	
Standing	6 (126/122)	0.004 (−0.03 to 0.04)	0.03/59.8		7 (137/106)	2.33 (−2.57 to 7.22)	4.8/56.5		0.81 (−1.08 to 2.70)	1.4/35.2	
Study design				0.07				0.88			0.08
Crossover	8 (263/265)	0.02 (−0.01 to 0.05)	0.03/80.1		11 (333/337)	−1.65 (−4.39 to 1.08)	2.8/49.1		−0.53 (−2.22 to 1.15)	1.9/60.5	
Parallel	19 (552/529)	0.07 (0.04 to 0.09)	0.04/87.8		23 (677/681)	−2.04 (−4.12 to 0.04)	3.6/65.2		−2.42 (−3.60 to −1.25)	1.8/48.3	
Trial quality factors											
Sample size				0.08				0.75			0.71
<50	16 (241/219)	0.03 (0.008 to 0.06)	0.04/82.1		20 (265/243)	−2.08 (−5.13 to 0.97)	5.2/62.6		−1.61 (−3.44 to 0.21)	3.2/66.2	
≥50	11 (574/575)	0.07 (0.05 to 0.10)	0.04/90.1		14 (745/774)	−1.75 (−3.48 to −0.01)	2.2/60.9		−2.01 (−3.28 to −0.74)	1.7/62.0	
Randomization				0.86				0.30			0.26
Success	19 (648/632)	0.06 (0.03 to 0.08)	0.05/88.5		25 (939/961)	−1.43 (−3.04 to 0.19)	2.7/59.4		−1.50 (−2.71 to 0.33)	2.2/68.5	
Failed	5 (143/138)	0.05 (−0.01 to 0.11)	0.06/87.9		2 (30/16)	5.10 (−3.96 to 14.2)	0.0/0.0		−4.28 (−7.19 to −1.37)	0.0/0.0	
Dropout rate				0.65				0.002			0.04
<10%	15 (588/578)	0.06 (0.03 to 0.9)	0.05/91.6		19 (726/772)	−3.29 (−5.12 to −1.47)	2.8/65.5		−2.63 (−3.92 to −1.35)	2.1/67.9	

(*Continued*)

Table. Continued

Subgroups	Serum Mg, mmol/L				SBP, mm Hg				DBP, mm Hg		
	No of Studies*	WMD (95% CI)	τ/I²	P†	No of Studies*	WMD (95% CI)	τ/I²	P†	WMD (95% CI)	τ/I²	P†
≥10%	6 (111/106)	0.04 (0.005 to 0.08)	0.04/65.7		6 (111/106)	5.30 (0.91 to 9.69)	0.0/0.0		0.99 (–1.28 to 3.25)	0.0/0.0	
Trial quality§				0.33				0.02			0.02
High	18 (510/497)	0.06 (0.04 to 0.09)	0.05/90.2		24 (643/658)	–3.37 (–5.34 to –1.40)	3.4/60.3		–2.50 (–3.65 to –1.36)	2.0/52.5	
Low	9 (306/296)	0.04 (0.02 to 0.05)	0.01/46.9		10 (367/360)	0.83 (–0.89 to 2.56)	1.1/16.2		0.35 (–1.45 to 2.15)	1.7/52.5	

τ is the estimate of between study SD. The percentages of I^2 around 25% (I^2=25), 50% (I^2=50), and 75% (I^2=75) indicate low, medium, and high heterogeneity, respectively. BP indicates blood pressure; DBP, diastolic blood pressure; Q1–Q4: quartile 1–quartile 4; RCT, randomized controlled trial; SBP, systolic blood pressure; and WMD, weighted mean difference.

*Number of studies (total number of participants in Mg supplemental group/placebo group).

†*P* values for interaction.

‡Medication history represented for taking antihypertensive or antidiabetic drugs during the period of study or off medication <1 mo before entering the current study.

§Trial quality was evaluated by Jadad score. Low: ≤3 and high: >3.

The BP-lowering effects of Mg supplementation were accompanied by elevated serum Mg levels. Greater reduction in both systolic and diastolic BPs also tended to be present in trials with high quality or low dropout rate. Taken together, our findings support a causal antihypertensive effect of Mg supplementation in adults.

The mechanisms of the antihypertensive effects of Mg have been confirmed by laboratory studies. Mg plays a role in the pathogenesis of hypertension mainly through alerting vascular smooth muscle cell function and the peripheral vascular resistance. As a cofactor of enzymes in signal transduction pathways involved in vascular contraction, Mg is able to inhibit the vasoconstriction induced by cytosolic accumulation of calcium concentrations.[30] And high levels of extracellular Mg were correlated with the improvements in hemodynamic status, such as

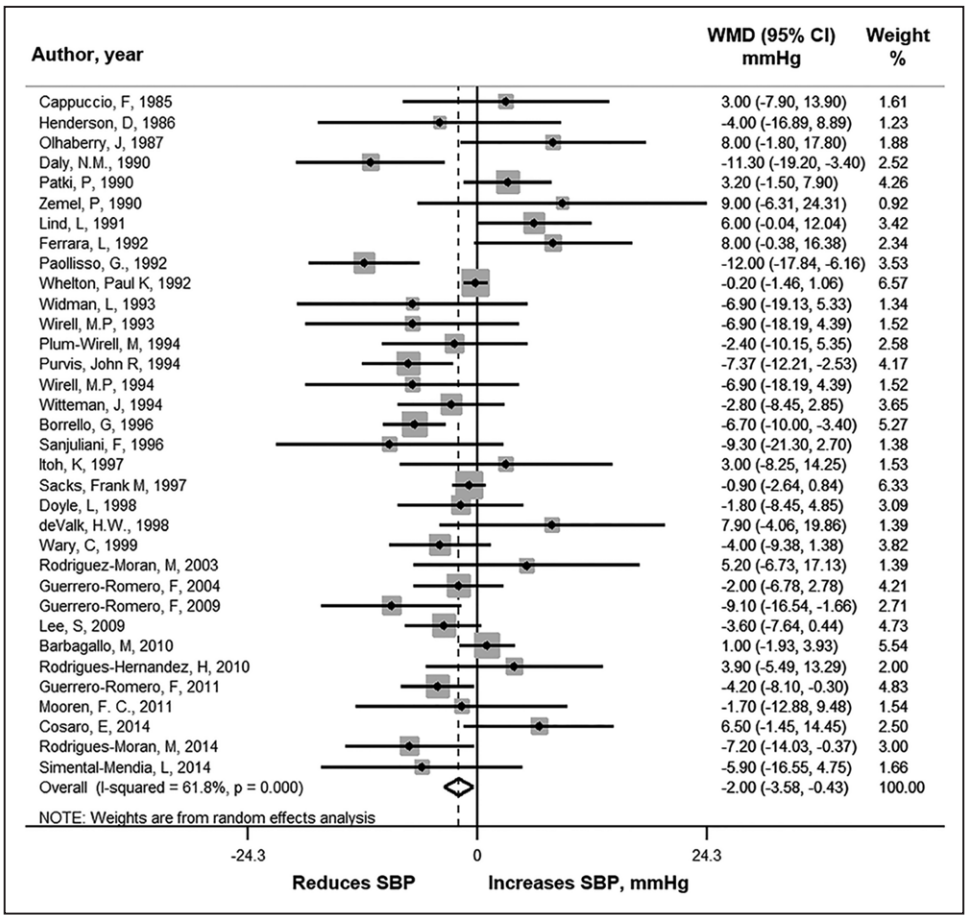

Figure 1. Forest plot of weighted mean differences (WMDs; 95% confidence intervals [CI]) for systolic blood pressure (SBP; mm Hg) responses to magnesium supplementation compared with placebo groups among 34 randomized controlled trials.

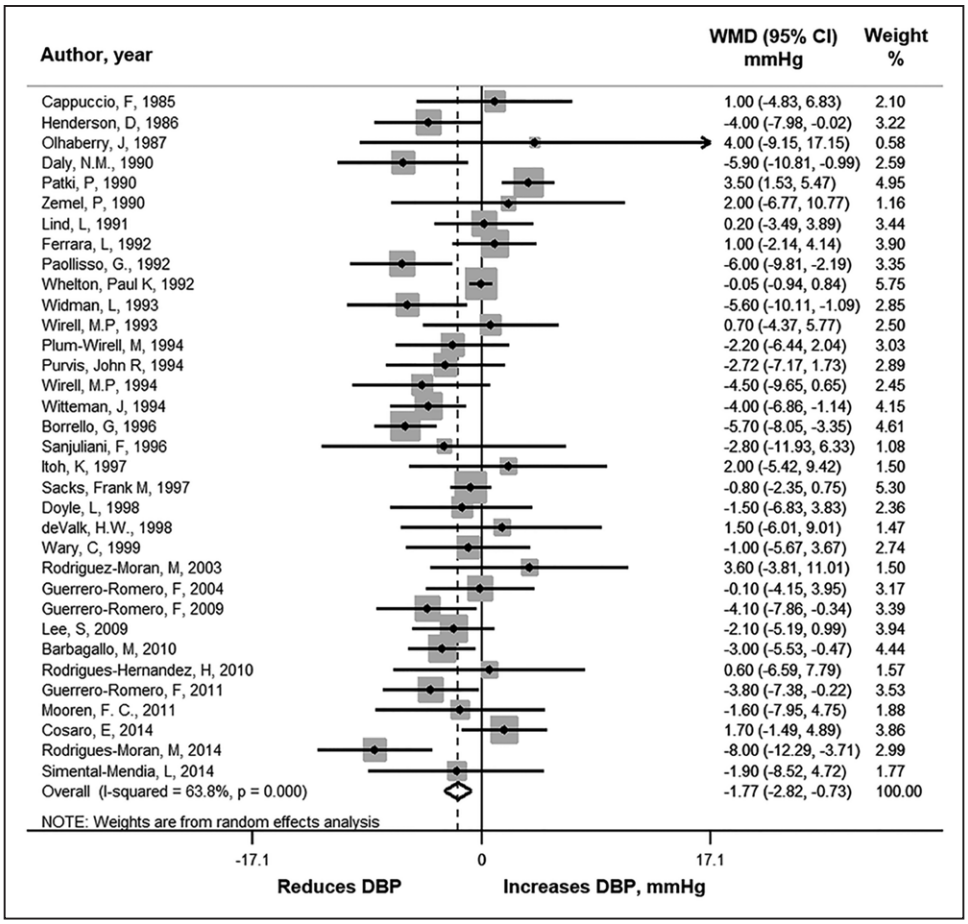

Figure 2. Forest plot of weighted mean differences (WMDs; 95% confidence intervals [CI]) for diastolic blood pressure (DBP; mm Hg) responses to magnesium supplementation compared with placebo groups among 34 randomized controlled trials.

blood flow, vascular resistance, and capacitance function of vessels, which contributes to the pathoetiology of hypertension.[31–34] Additionally, Mg has shown its antioxidant benefits in the prevention of hypertension through attenuating the damage of vasculature from oxidative stress and preventing vascular injury.[5,6]

Although accumulating evidence from such studies has indicated that low dietary or circulating Mg may be related to the development of hypertension because of its calcium antagonist and endothelial effects,[35] epidemiological evidence for a relationship between Mg intake and hypertension has been controversial. Several observational studies have suggested an inverse association between Mg intake and BP,[10,36–39] although evidence from observational studies is indirect because of potential selection bias, residual confounding, measurement errors of Mg intake, and statistical uncertainty because of highly correlated dietary or lifestyle factors. Many small and short-term randomized trials have been conducted to directly test the effect of Mg supplementation in normotensive and hypertensive participants, but those results were inconsistent and inconclusive. Nonsignificant associations between dietary Mg and systolic or diastolic BP were found based on a meta-analysis of 16 RCTs.[40] In contrast, Jee et al[12] showed a small overall dose-dependent BP reduction with Mg supplementation from a meta-analysis involving 20 small randomized trials (13–461 participants per trial) of short duration (3–24 weeks per trial). A recent meta-analysis of 22 trials, including 1220 normotensive or hypertensive patients, reported a mean reduction of 2 to 3 mm Hg in systolic BP and of 3 to 4 mm Hg in diastolic BP.[14] The results were consistent with our findings of 2.00/1.78 mm Hg reduction in systolic/diastolic BP from 34 randomized, double-blind, placebo-controlled trials. Our data indicated that provision of Mg may slightly lower BP and might be effective in preventing hypertension in the general population.

Furthermore, our pooled results from 16 trials among hypertensive patients showed a 2.11 mm Hg (95% CI, 4.17–0.05) decrease in diastolic BP but a nonsignificant decrease in systolic BP (−2.16 mm Hg; 95% CI, −5.71 to 1.40). A significant reduction in diastolic BP but not in systolic BP was consistently identified by a Cochrane review of 12 RCTs among hypertensive patients.[13] In our study, data from 7 trials among 136 treated patients (those taking antihypertensive or diabetic drugs) suggest that both systolic (5.69 mm Hg) and diastolic (2.55 mm Hg) BP were significantly reduced. This discrepancy between treated and untreated patients might be partially caused by possibly lower baseline Mg status among treated patients, because loop and thiazide diuretics, mainly used among hypertensive and diabetic patients, may deplete potassium and Mg.[11] On average, serum Mg was 0.74 mmol/L for treated patients, slightly lower than the current lower limits of the clinical normal range for serum Mg, 0.75 to 0.96 mmol/L.[41] Moreover, our subgroup analysis indicated that the antihypertensive effect of Mg was significant only among the subgroup with Mg deficiency. Current evidence has also suggested that

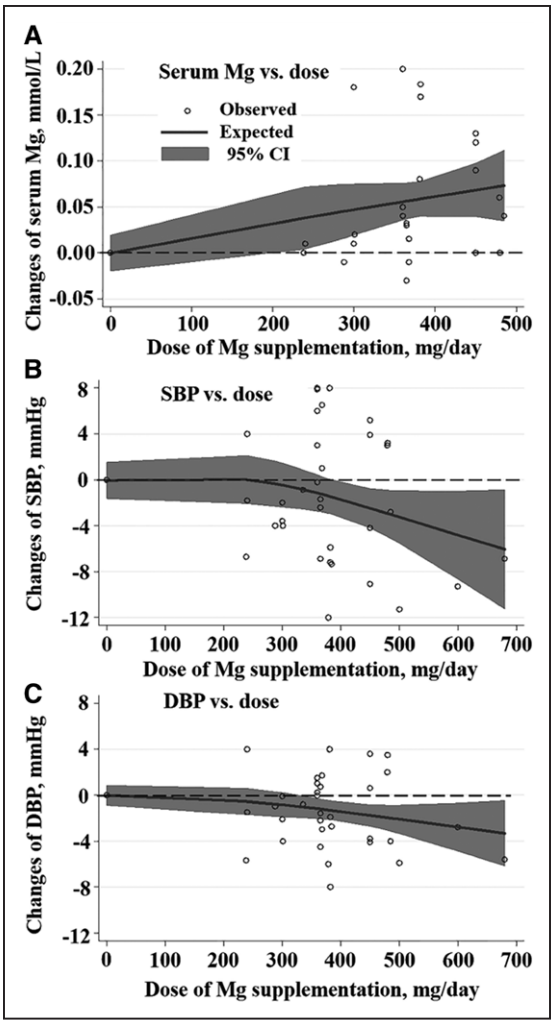

Figure 3. Serum magnesium (Mg; **A**), systolic blood pressure (SBP; **B**), and diastolic blood pressure (DBP; **C**) changes in response to Mg with different doses (elemental Mg, mg/d). The nonlinear relation was fitted using a restricted cubic spline regression curve among 34 randomized controlled trials.

the antihypertensive effect of Mg might be valid only among patients with Mg deficiency or insufficiency.[42] However, this conclusion needs to be confirmed by further specific research.

Our dose–response analysis of 34 trials provided sufficient power to depict the dose–response analysis for both BPs and serum Mg. Because of relative low power and limited information,[13] a previous meta-regression analysis of 14 double-blind randomized trials showed that a 240 mg/d increase in Mg intake was associated with a nonsignificant decrease in systolic BP and diastolic BP among hypertensive patients.[12] In addition, a relative large numbers of identified RCTs let it possible to explore the possible dose and time responses of BPs to Mg supplementation. And we found curvilinear dose- and time-dependent relationships for Mg supplementation and BPs and serum Mg levels. Furthermore, we quantified the associations between changes in serum Mg and BPs based on data from 27 of the 34 trials reported changes in serum Mg levels in our meta-analysis; we found that a 0.1 mmol/L increment in serum Mg was associated with a 2.26 mm Hg reduction in diastolic BP. However, the association of changes in serum Mg with systolic BP was nonsignificant. Meanwhile, the significant relations between elevated serum Mg and BP-lowering effects indirectly supported the causal hypothesis of antihypertensive effect of Mg.

Of note, there was considerable heterogeneity across the Mg studies in terms of trial quality, sample sizes, and participant characteristics, any of which could influence the accuracy of the pooled estimates. Although previous meta-analyses noted that heterogeneities might be induced by sex,[13] study location, and types of study design,[14] we found no evidence of modification from these factors on the effects of Mg supplementation on BPs. Nonsignificant heterogeneities were also found for age, Mg supplements, and methods of BP measurements. The results from high-quality trials (Jadad >3) or trials with low dropout rates (<10%) were more likely to show a significant reduction in both systolic and diastolic BP after Mg supplementation than trials with low-quality scores and high dropout rates. These findings provide strong support for the robustness of our results, indicating the BP-lowering effects of Mg.

A major strength of this meta-analysis is the inclusion of only randomized double-blind placebo-controlled trials. With 34 trials,

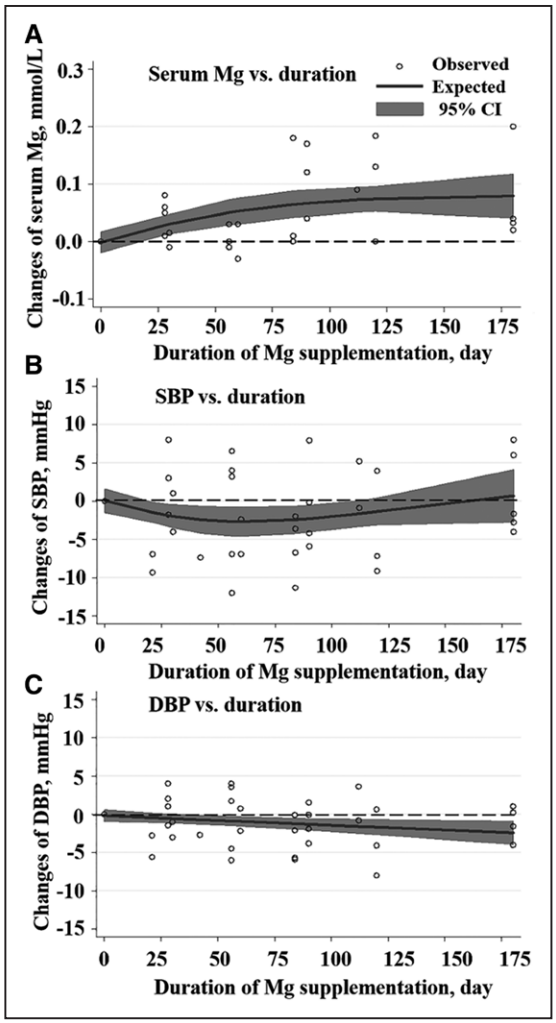

Figure 4. Serum magnesium (Mg; **A**), systolic blood pressure (SBP; **B**), and diastolic blood pressure (DBP; **C**) changes in response to Mg with different duration (day). The nonlinear relation was fitted using a restricted cubic spline regression curve among 34 randomized controlled trials.

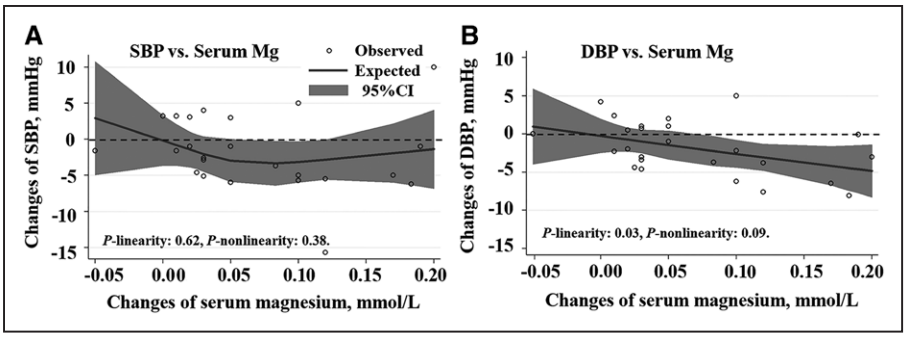

Figure 5. Systolic blood pressure (SBP; **A**) and diastolic blood pressure (DBP; **B**) changes vs serum magnesium (Mg) changes (mmol/L) after Mg supplementation among 20 randomized controlled trials.

we achieved sufficient power to capture overall effects and assess the dose- and time-dependent relationships between BPs and Mg supplementation. Major sources of heterogeneity were explored by including 15 factors, including age; sex; study location; Mg formulation; dosage; trial duration; baseline Mg and BP status; antihypertensive or diabetic medication use history; methods, time, and position of BP measurements; and crossover design.

However, several limitations merit consideration. First, most trials included were small with relatively high dropout rates. Second, we used serum Mg to reflect Mg status, although it may not be an optimally sensitive biomarker of Mg status in the human body,[43] because only 0.3% of total body Mg is present in serum, and serum Mg levels are normally maintained within a very narrow range. Therefore, the measurement of serum total Mg may not accurately reflect Mg bioavailability. Third, the benefits of Mg supplementation may be most dramatic in individuals with insufficient Mg status and might have enhanced effects by antihypertensive or antidiabetic drugs. However, we have insufficient data to test this hypothesis. Also, detailed information on diet and lifestyles of subjects is unavailable. Fourth, significant heterogeneity was present among RCTs; despite this, results were generally consistent across trials. Furthermore, our subgroup and sensitivity analysis results suggested that overall treatment effects did not differ appreciably by most specified factors. Fifth, nearly all identified trials measured BP by sphygmomanometer or automatic monitor; there are spare studies using 24-hour ambulatory BP monitoring. Sixth, lack of detailed information cannot allow us to disentangle acute versus chronic effects by taking Mg supplements. Seventh, the observational nature of our subgroup analysis and spline regression analysis requires cautious interpretation of their results. Also, our subgroup analyses stratified by study-level covariates, such as sex proportions and mean or median of ages, may be prone to aggregation bias or ecological bias because study-level covariates with limited variability may not precisely represent those at the individual or patient levels. We cannot completely rule out the possibility of a nonrandom impact of heterogeneity on the summary estimates, which cannot be easily handled by traditional statistical approaches. And residual heterogeneity may still exist after considering these possible factors. Finally, as in any meta-analysis, publication bias is possible.

Perspectives

The meta-analysis, based on evidence from 34 randomized, double-blind, placebo-controlled trials, showed a significant antihypertensive effect of Mg supplementation on both systolic and diastolic BP among normotensive or hypertensive adults. The significant BP reduction by Mg supplementation was accompanied by elevated levels of serum Mg and also tended to be evident in trials with high quality or low dropout rate, indicating a causal BP-lowering effect of Mg supplementation. Our findings suggested that oral Mg supplements can be recommended for the prevention of hypertension or as adjuvant antihypertensive therapy, although future rigorously designed RCTs with BP assessment as primary outcomes are warranted to yield confirmatory evidence.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This study is much larger with 34 randomized, double-blind, placebo-controlled trials than previous meta-analyses. Therefore, we were able to achieve sufficient power to detect an overall modest effect and reliably assess the dose- and time-dependent relationships between magnesium (Mg) supplementation and blood pressure changes.
- Major sources of heterogeneity were explored thoroughly by subgroup analyses stratified by potential factors.
- Overall trial quality was qualitatively evaluated by Agency for Healthcare Research and Quality criteria and quantitatively assessed by the Jadad score. Also, we further performed subgroup analyses to evaluate robustness of the results.
- Considering both compliance and effectiveness, we evaluated changes in serum Mg produced by Mg supplementation and found a close association with concomitant blood pressure reductions, indicating a causal effect.

What Is Relevant?

- The findings support that Mg supplementation provides a moderate blood pressure–lowing effect among normotensive or hypertensive adults.
- Future large and rigorously designed trials among participants at risks for Mg insufficiency and hypertension will be required to confirm the antihypertensive effects of Mg supplementation.

Summary

- This meta-analysis, based on reliable data from 34 rigorously designed randomized controlled trials, provided robust evidence to support a causal effect of Mg supplementation on lowering blood pressures in adults.

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Xi Zhang[1], Yufeng Li[2*], Liana C. Del Gobbo[3], Andrea Rosanoff[4], Jiawei Wang[5], Wen Zhang[6], Yiqing Song[1]

Affiliations:

1. Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, IN, USA.
2. Department of Endocrinology, Beijing Pinggu Hospital, Beijing, China.
3. Department of Medicine, Division of Cardiovascular Medicine, Stanford University, Stanford, CA, USA.
4. Center for Magnesium Education and Research. Pahoa, HI, USA.
5. Douglas Mental Health University Institute, McGill University, Montreal, Quebec, Canada.
6. Department of Epidemiology, School of Medicine, Fukushima Medical University, Fukushima, Japan.

Short title: Magnesium and Blood Pressure

Correspondence to Yiqing Song, MD, ScD, Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, 1050 Wishard Blvd., RG 5117, Indianapolis, IN 46202-2782.

Tel: 317-274-3833; Fax: 317-274-3443; E-mail: yiqsong@iu.edu

Table S1. Characteristics of 34 articles included in the meta-analysis

Author, year	Country	Participants status	Total, N_t/N_p	Anti-HTN medication	Age, years	Sex, %women	Mg formulation	Dose, mg/day/ Duration, day	Crossover/ Measures of BP
Cappuccio, F, 1985	US	Mild to moderate hypertension	17, 9/8	Off medicine ≥2 month	Range: 33-66	Both, 47%	Mg asparate *	360/28	YES/Spygmomanometer
Henderson, D, 1986	Denmark	Hypertension	41, 21/20	NR	Mean: 62	Both, NR	MgO *	301/180	NO/NR
Olhaberry, J, 1987	Uruguay	Mild esential hypertension	40, 20/20	No medication	Range: 24-64	Female	$MgCl_2$ *	380.88/28	NO/Sphygmomanometer
Patki, P, 1990	India	Mild hypertension	37, 37/37	Off medicine ≥1 month	Mean: 49.9±7.6	Both, 78%	$MgCl_2$ *	480/56	YES/Spygmomanometer
Zemel, P, 1990	US	Mild hypertension	13, 7/6	Off medicine ≥3 months	Range: 20-69	Both, 14%	Mg asparate -HCl *	960/90	NO/Automatic BP monitor
Daly, N.M., 1990	Germany	Borderline hypertension	40, 20/20	No medication	Mean: 59	Both, 55%	MgO	500/84	NO/NR
Lind, L, 1991	Sweden	Hypertension	71, 49/22	No medication	Mean: 61	NR	Mg lactate Mg citrate	360/180	NO/Spygmomanometer
Ferrara, L, 1992	Italy	Mild to moderate hypertension	14, 7/7	No medication	Range: 40-60	Both, 43%	Mg pidolate *	360/180	NO/Automatic BP monitor
Whelton, Paul K, 1992	US	Healthy	461, 227/234	No medication	Range: 30-54	Both, 31%	NR *	360/180	YES/Sphygmomanometer
Paolisso, G., 1992	Italy	Lower arterial blood pressure	18, 9/9	Thiazide	Mean: 64±3	Both, 50%	Mg pidolate	379/56	NO/NR
Widman, L, 1993	Sweden	Mild hypertension	17, 17/17	Off medicine ≥4 months	Mean: 50±6	Both, 12%	$Mg(OH)_2$	360/21	YES/Sphygmomanometer
Wirell, M.P, 1993	Sweden	Mild to moderate hypertension	36, 18/18	Thiazide	Range: 29-62	Both, 47%	Mg asparate-HCl *	365/60	YES/NR

Table S1. Characteristics of 34 articles included in the meta-analysis

Author, year	Country	Participants status	Total, N_t/N_p	Anti-HTN medication	Age, years	Sex, %women	Mg formulation	Dose, mg/day/ Duration, day	Crossover/ Measures of BP
Wirell, M.P, 1994	Sweden	Moderate hypertension	39, 21/18	Beta-block	Range: 26-69	NR	Mg asparate -HCl *	365/56	YES/Spygmomanometer
Plum-Wirell, M, 1994	Sweden	Mild to moderate untreated hypertention	39, 39/39	No medication	Range: 20-59	Both, 38%	Mg asparate-HCl *	365/60	YES/Spygmomanometer
Witteman, J, 1994	Belgium	Mild to moderate hypertension	91, 47/44	No medication	Range: 35-77	Female	Mg asparate-HCl *	485/180	NO/Sphygmomanometer
Purvis, John R, 1994	US	NIDDM	28, 28/28	Dietary control and hypoglycemic	Range: 28-84	Both, 86%	$MgCl_2$	384/42	YES/Automated BP mornitor
Borrello, G, 1996	Italy	Mild hypertension	83, 42/41	No medication	Mean: 42	Both, 64%	MgO *	238.32/84	NO/24-h BP, Ambulatory BP
Sanjuliani, F, 1996	Brazil	Mild to moderate hypertension	15, 15/15	NR	Range: 36-65	Both, 53%	MgO	600/21	YES/Automatic BP mornitor
Itoh, K, 1997	Japan	Healthy	33, 23/10	No medication	Mean: 65	Both, 67%	$Mg(OH)_2$ *	479.5/28	NO/Automatic BP mornitor
Sacks, Frank M, 1998	US	Healthy	48, 50/103	No medication	Mean: 39	Female	Mg lactate	336/112	NO/24-h BP, Ambulatory BP
deValk, H.W., 1998	Netherlands	T2DM	50, 25/25	Insulin and other anti-diabete medicine	Mean: 63	Both, 44%	Mg asparate-HCl *	360/90	NO/NR
Doyle, L, 1999	Ireland	Healthy	26, 13/13	No medication	Range: 20-28	Female	$Mg(OH)_2$ *	240/28	YES/Sphygmomanometer
Wary, C, 1999	Belgium	Healthy	30, 15/15	No medication	Range: 28-35	Male	Mg lactate *	288/30	NO/NR
Rodriguez-Moran, M, 2003	Mexico	T2DM and decreased serum Mg	63, 32/31	Glibenclamide	Mean: 57	NR	$MgCl_2$ *	450/112	NO/NR

Table S1. Characteristics of 34 articles included in the meta-analysis

Author, year	Country	Participants status	Total, N_t/N_p	Anti-HTN medication	Age, years	Sex, %women	Mg formulation	Dose, mg/day/ Duration, day	Crossover/ Measures of BP
Guerrero-Romero, F, 2004	Mexico	Healthy	63, 32/31	No medication	Mean: 43	Both, NR	$MgCl_2$ *	300/84	NO/NR
Lee, S, 2009	South Korea	Healthy	155, 75/80	No medication	Range: 30-60	Both, 50%	MgO *	300/84	NO/Automated BP mornitor
Guerrero-Romero, F, 2009	Mexico	Diabetic hypertension & lower serum Mg	79, 40/39	Captopril	Range: 40-75	Both, 52%	$MgCl_2$ *	450/120	NO/Baumanometer & stethoscope
Barbagallo, M, 2010	Italy	Diabetic patients	60, 30/30	NR	Mean: 71.1±6.1	Both, 42%	Mg pidolate *	368/30	NO/Sphygmomanometer
Rodrigues-Hernandez, H, 2010	Mexico	Healthy	30, 20/18	No medication	Range: 30-65	Female	$MgCl_2$ *	450/120	NO/NR
Mooren, F. C., 2011	Germany	Healthy	47, 25/22	No medication	Range: 30-70	NR	Mg asparate-HCl *	365/180	NO/Sphygmomanometer
Guerrero-Romero, F, 2011	Mexico	Healthy	97, 49/48	No medication	Range: 40-65	Both, 41%	$MgCl_2$ *	450/90	NO/Sphygmomanometer
Cosaro, E, 2014	Italy	Healthy	14, 14/14	No medication	Range: 23-33	NR	Mg pidolate *	368/28	YES/Seminautomatic oscillometric device
Rodrigues-Moran, M, 2014	Mexico	Healthy	47, 24/23	No medication	Range: 20-60	Both, 66%	$MgCl_2$ *	382/120	NO/NR
Simental-Mendia, L, 2014	Mexico	New diagnosed prediabetes and hypomagnesemis	57, 29/28	NR	Range: 18-65	Both, 58%	$MgCl_2$ *	382/90	NO/NR

NIDDM, non-insulin dependent diabetes mellitus; BP, blood pressure; T2DM, type 2 diabete mellitus; NR, not reported; HTN, hypertension.

N_t: No. of participants in treatment group; N_p: No. of participants in placebo group. * Studies reported the serum Mg levels.

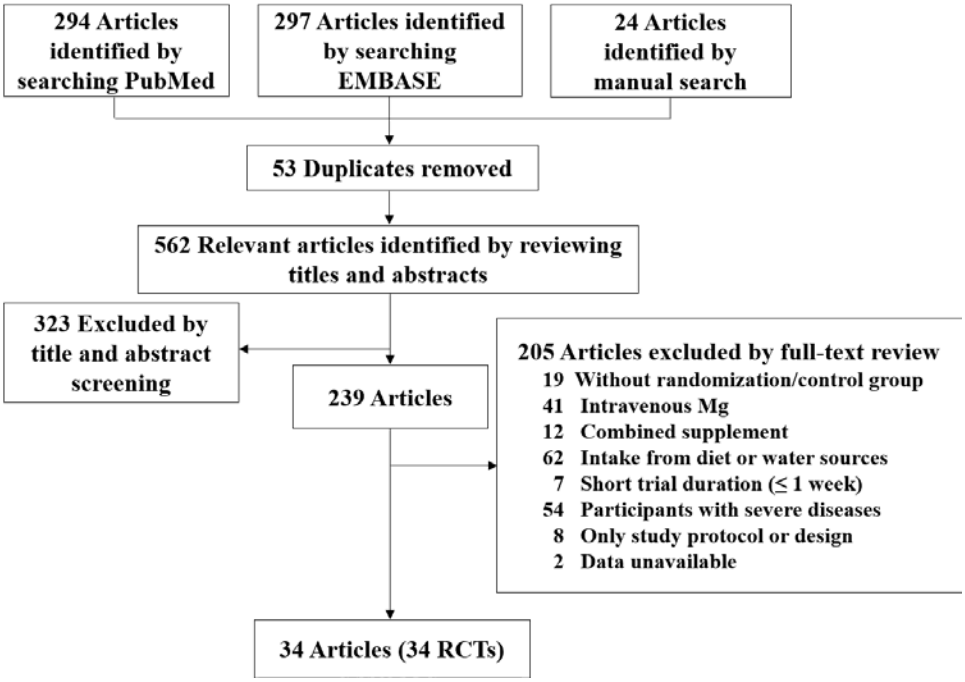

Figure S1. Flowchart of literatures search and study selection

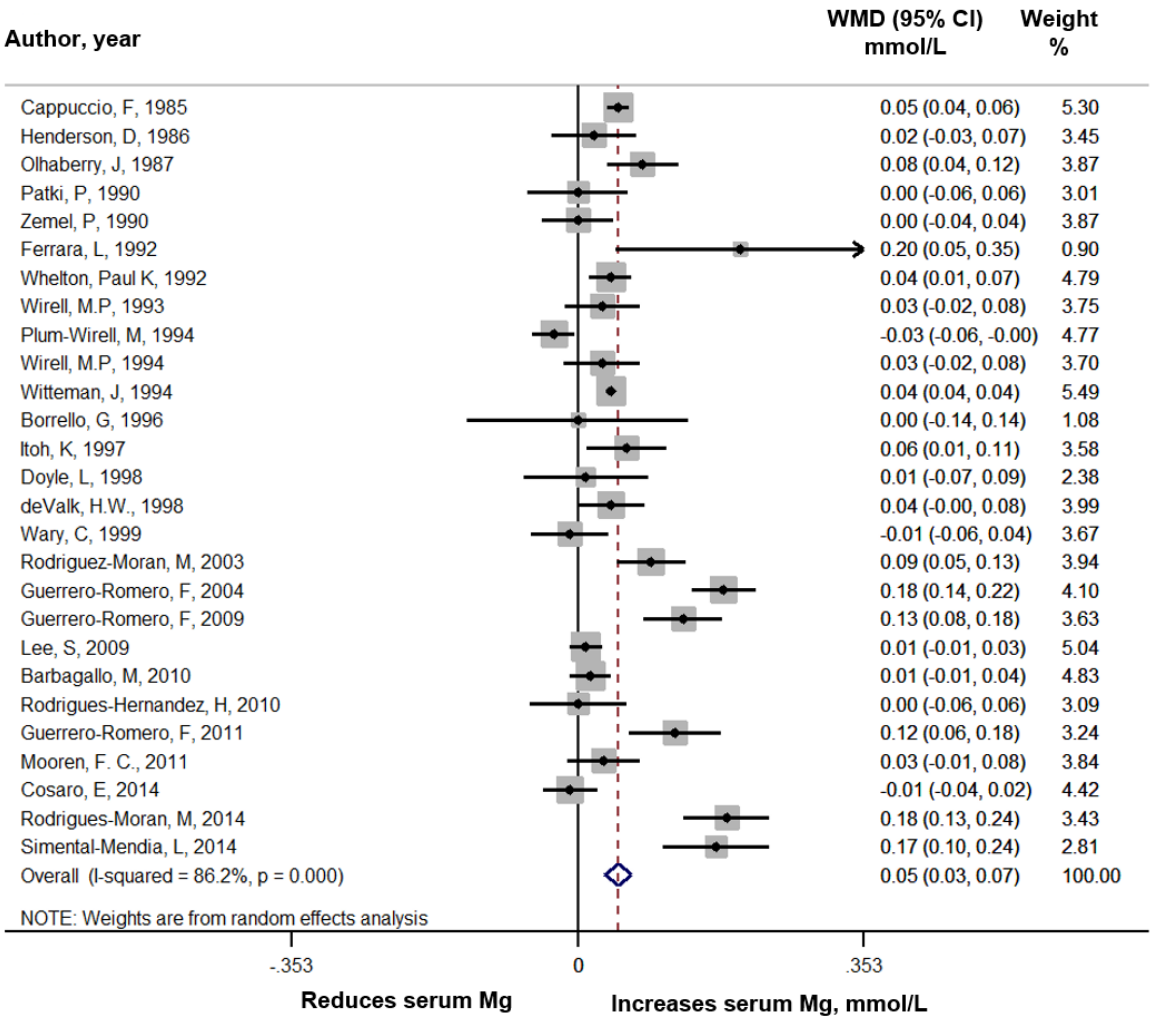

Figure S2. Forest plot of WMDs (95% CI) for serum Mg levels (mmol/L) responses to Mg supplementation compared with placebo groups among 27 RCTs.

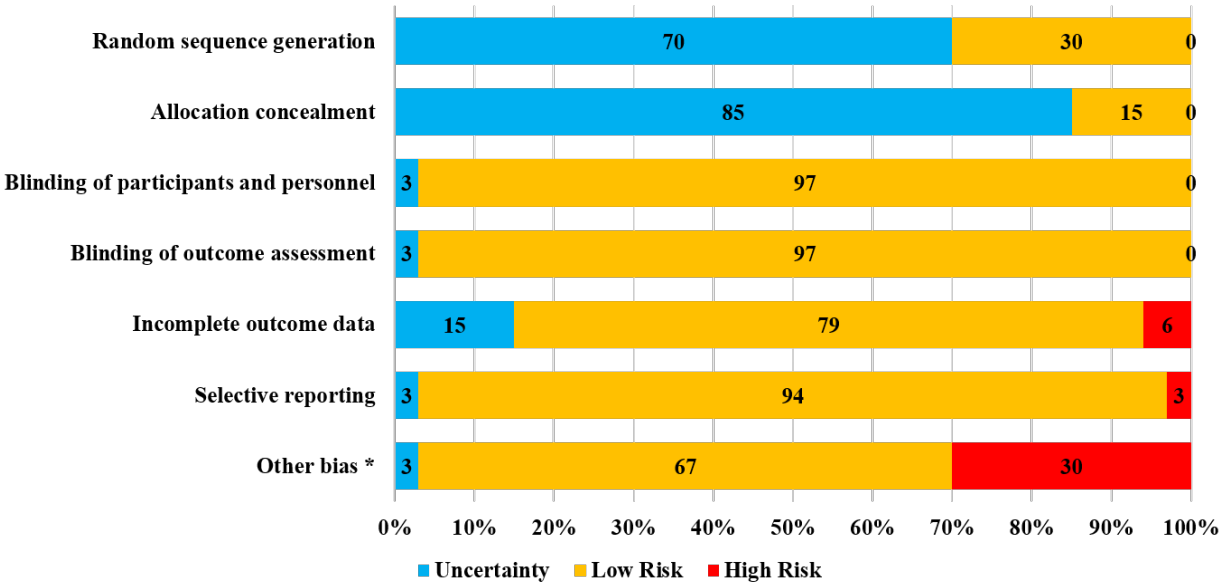

Figure S3. Quality of 34 trials in the meta-analysis assessed by AHRQ criteria.
* Other bias: Other important concerns about bias was not covered in the other items.