

Effects of Magnesium Supplementation in Hypertensive Patients

Assessment by Office, Home, and Ambulatory Blood Pressures

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Abstract—An increase in magnesium intake has been suggested to lower blood pressure (BP). However, the results of clinical studies are inconsistent. We studied the effects of magnesium supplementation on office, home, and ambulatory BPs in patients with essential hypertension. Sixty untreated or treated patients (34 men and 26 women, aged 33 to 74 years) with office BP >140/90 mm Hg were assigned to an 8-week magnesium supplementation period or an 8-week control period in a randomized crossover design. The subjects were given 20 mmol/d magnesium in the form of magnesium oxide during the intervention period. In the control period, office, home, and average 24-hour BPs (mean±SE) were 148.6±1.6/90.0±0.9, 136.4±1.3/86.8±0.9, and 133.7±1.3/81.0±0.8 mm Hg, respectively. All of these BPs were significantly lower in the magnesium supplementation period than in the control period, although the differences were small (office, 3.7±1.3/1.7±0.7 mm Hg; home, 2.0±0.8/1.4±0.6 mm Hg; 24-hour, 2.5±1.0/1.4±0.6 mm Hg). Serum concentration and urinary excretion of magnesium increased significantly with magnesium supplementation. Changes in 24-hour systolic and diastolic BPs were correlated negatively with baseline BP or changes in serum magnesium concentration. **These results indicate that magnesium supplementation lowers BP in hypertensive subjects and this effect is greater in subjects with higher BP. Our study supports the usefulness of increasing magnesium intake as a lifestyle modification in the management of hypertension, although its antihypertensive effect may be small.** (*Hypertension*. 1998;32:260-265.)

Key Words: hypertension, essential ■ magnesium ■ nonpharmacological treatment ■ blood pressure ■ blood pressure, ambulatory

Magnesium is related to various physiological functions, including cardiovascular regulation. It may play an important role in control of neuronal activity, cardiac excitability, neuromuscular transmission, muscular contraction, vascular tone, BP, and peripheral blood flow.¹ Mg ions compete with Ca ions for membrane-binding sites, lower levels of intracellular Ca²⁺, and cause vasodilation. It has been suggested that deficiency in Mg and abnormalities in Mg metabolism play pathophysiological roles in ischemic heart disease, congestive heart failure, sudden cardiac death, arrhythmias, preeclampsia and eclampsia, insulin resistance and diabetes, and hypertension.¹

An inverse relationship between dietary Mg intake and the level of BP or the prevalence of hypertension has been observed in epidemiological studies.²⁻⁴ It has also been shown that hypertensive patients often have reduced serum and intracellular levels of Mg²⁺ compared with normotensive subjects.^{5,6} Measurements of serum ionized Mg and intracellular free Mg²⁺ may provide better estimation for the Mg deficiency than conventional measurement of serum Mg.^{6,7} In experimental studies, dietary Mg deficiency raises BP of normotensive animals, whereas Mg supplementation lowers

BP in hypertensive rats.^{8,9} However, the results of clinical studies on the effects of Mg supplementation in hypertensive patients and subjects with high normal BP have been inconsistent. Significant reductions in BP have been shown in several studies,¹⁰⁻¹² but not in others.^{13,14} Although adequate dietary intake of Mg was recommended in the report of the Joint National Committee,¹⁵ increasing Mg intake is not accepted as a general application in the treatment of hypertension.¹⁶

Earlier clinical studies concerning Mg supplementation relied on casual BP measurements. Monitoring of 24-hour ambulatory BP and self-measurement of BP at home have advantages compared with casual BP measurement because they provide multiple BP records, have good reproducibility, and eliminate observer bias and the placebo effect.¹⁷ These methods appear to be particularly useful in the evaluation of nonpharmacological interventions, as we have shown.^{18,19} To our knowledge, only 1 study used ambulatory BP monitoring to assess the effects of Mg supplementation,²⁰ and the effects of Mg on home BP have not been reported. In the present study, we investigated the effects of Mg supplementation on 24-hour ambulatory BP and home BP, as well as casual office

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Selected Abbreviations and Acronyms

BP	= blood pressure
DBP	= diastolic blood pressure
NMR	= nuclear magnetic resonance
SBP	= systolic blood pressure

BP, in hypertensive patients who were untreated or insufficiently treated in a randomized crossover design.

Methods

Subjects

Sixty-two Japanese men and women with mild to moderate essential hypertension participated in this study. They were 35 to 74 years old, either treated or untreated, and had office SBP >140 mm Hg and/or DBP >90 mm Hg on at least 2 occasions before entering the study protocol. Two patients withdrew from the study because of gastrointestinal symptoms (diarrhea) during Mg supplementation. The remaining 60 subjects completed the study protocol.

The clinical characteristics of the 60 patients are shown in Table 1. Twenty subjects were untreated, while 40 subjects were treated with antihypertensive drugs. Among the treated subjects, 18 were receiving monotherapy and 22 were receiving combination therapy. Ca antagonists were the most frequently prescribed drugs (n=30), followed by β -blockers (n=14), angiotensin-converting enzyme inhibitors (n=9), diuretics (n=6; 5 thiazide, 1 spironolactone), and α -blockers (n=5). Antihypertensive therapy was continued without any alterations throughout the study protocol.

Protocol

The study protocol was approved by the Clinical Research Committee of our institute. Informed consent was given by each subject before participation in this study. An 8-week Mg supplementation period and an 8-week control period were assigned in a randomized crossover manner. Thirty subjects entered the control period first, and the other 30 subjects entered the Mg period first. During the Mg supplementation period, 20 mmol/d (480 mg) Mg was given in the form of MgO (400 mg BID) to each subject. Placebo was not given during the control period because the placebo effect is usually negligible in the monitoring of ambulatory or home BP,^{17,21} and the majority of subjects were already taking antihypertensive drugs.

Casual office BP and 24-hour ambulatory BP were measured at the end of the control and Mg supplementation periods. Home BP was measured throughout the study protocol. Blood samples and 24-hour urine samples were collected at the end of each period.

Measurements

Office BP was measured twice with the subject in the sitting position by a physician with a mercury sphygmomanometer. Home BP was measured by the patients in the sitting position 3 times in the early morning and also in the late evening with semiautomatic devices using the oscillometric method. Ambulatory BP was measured every

TABLE 1. Clinical Characteristics of Study Subjects

Parameter	
Age, y	35–74 (58.1±1.1)
Gender, M/F	34/26
Body weight, kg	63.8±1.3
Body mass index, kg/m ²	24.7±0.4
Antihypertensive drugs	Yes 40, No 20
Drinking habit*	Yes 25, No 35

*Yes indicates regular drinkers (≥ 1 drink/d); no, abstainers or occasional drinkers.

TABLE 2. Serum and Urinary Electrolyte Levels in Control and Mg Supplementation Periods

Parameter	Control Period	Mg Period
Serum		
Na, mmol/L	142.1±0.2	142.1±0.2
K, mmol/L	4.25±0.05	4.36±0.05
Ca, mmol/L	2.37±0.02	2.36±0.02
Mg, mmol/L	0.84±0.01	0.89±0.01*
Urine		
Na, mmol/d	182.5±9.5	188.7±9.9
K, mmol/d	54.2±2.0	54.7±2.1
Ca, mmol/d	4.95±0.32	5.10±0.35
Mg, mmol/d	2.92±0.13	4.67±0.21*
Cr, g/d	1.20±0.05	1.21±0.05

Cr indicates creatinine. * $P < 0.001$ between the 2 periods.

30 minutes for 25 to 26 hours by the oscillometric method using the TM-2421 (A&D Co Ltd). Accuracy and performance of this device have been demonstrated previously.²² The accuracy of each recorder was also checked by simultaneous measurement with a mercury sphygmomanometer, and all recorders showed a difference of <10 mm Hg. The same recorder was used in each subject to avoid errors due to differences in equipment. Serum and urinary electrolyte levels were determined with a TBA-80 M autoanalyzer (Toshiba).

Data Analysis

Averages of 2 measurements were used for analysis of office BP. For home BP, averages of the records for the last 7 days in each period were used. The first 1-hour record of ambulatory BP was discarded for the analysis of 24-hour BP because it may be substantially higher than the usual BP. The daytime BP was defined as that from 6:30 AM to 10 PM, and the nighttime BP was defined as that from 10:30 PM to 6 AM in this study.

Data are expressed as mean±SEM. Student's paired or unpaired *t* test was used for comparison of 2 groups of data. Linear regression analysis was used to assess correlations between 2 parameters.

TABLE 3. Office, Home, and 24-Hour Ambulatory BP in Control and Mg Supplementation Periods

Parameter, mm Hg	Control Period	Mg Period	Difference
Office			
SBP	148.6±1.6	144.9±1.7	3.7±1.3†
DBP	90.0±0.9	88.3±0.9	1.7±0.7*
Home			
SBP	136.4±1.3	134.4±1.4	2.0±0.8*
DBP	86.8±0.9	85.4±0.8	1.4±0.6*
24-h			
SBP	133.7±1.3	131.2±1.1	2.5±0.8†
DBP	81.0±0.8	79.6±0.8	1.4±0.6*
Day			
SBP	137.7±1.2	135.2±1.3	2.5±1.1*
DBP	84.0±0.8	82.5±0.9	1.5±0.7*
Night			
SBP	125.9±1.9	123.4±1.5	2.5±1.3
DBP	74.8±1.1	73.6±0.9	1.2±0.7

Day indicates 6:30 AM to 10 PM; Night, 10:30 PM to 6 AM.

* $P < 0.05$, † $P < 0.01$.

TABLE 4. Body Weight, Electrolyte Level, and BP in Control and Mg Supplementation Periods in Men and Women

Parameter	Men		Women	
	Control	Mg Supplement	Control	Mg Supplement
Body weight, kg	68.8±1.6	68.7±1.7	57.4±1.4	57.4±1.5
Serum				
Na, mmol/L	141.6±0.3	141.7±0.2	142.7±0.3	142.5±0.4
K, mmol/L	4.27±0.06	4.30±0.06	4.24±0.10	4.44±0.07
Ca, mmol/L	2.36±0.02	2.33±0.02	2.37±0.02	2.38±0.02
Mg, mmol/L	0.83±0.01	0.90±0.01‡	0.85±0.01	0.88±0.01†
Urine				
Na, mmol/d	199.5±14.2	204.6±15.5	162.6±11.0	167.8±9.7
K, mmol/d	56.2±2.8	56.8±2.9	52.0±3.1	52.4±3.0
Ca, mmol/d	5.08±0.52	5.20±0.47	4.80±0.41	4.98±0.53
Mg, mmol/d	3.17±0.21	4.60±0.29‡	2.70±0.14	4.70±0.22‡
Cr, g/d	1.43±0.06	1.42±0.07	0.92±0.04	0.94±0.04
Office BP, mm Hg				
SBP	145.0±1.8	140.9±2.0*	153.5±2.6§	150.1±2.7§
DBP	89.4±0.9	86.4±1.1*	90.5±1.7	90.0±1.5
Home BP, mm Hg				
SBP	136.3±1.9	134.0±1.9*	136.5±2.1	134.9±2.0
DBP	87.2±1.3	85.7±1.0*	86.4±1.5	85.2±1.4
24-h BP, mm Hg				
SBP	135.4±1.8	131.6±1.6*	131.6±1.7	130.8±1.6
DBP	82.6±1.0	80.5±1.0*	78.8±1.3	78.4±1.3

* $P<0.05$, † $P<0.01$, ‡ $P<0.001$ between the control and Mg periods; § $P<0.05$, || $P<0.001$ between men and women.

Multiple regression analysis was used to identify independent determinants for the change in BP with Mg supplementation. A value of $P<0.05$ was considered statistically significant. Analyses were performed using StatView software (Abacus Concepts Inc).

Results

Serum and urinary electrolyte levels in the control and Mg supplementation periods are shown in Table 2. Serum concentration and urinary excretion of Mg increased significantly after Mg supplementation. The average change in serum Mg was 6%, and that in urinary Mg was 60%. Serum and urinary levels of Na, K, and Ca, as well as urinary creatinine excretion, were similar between the 2 periods.

Table 3 shows office, home, and ambulatory BPs in the control and Mg supplementation periods. These levels correlated significantly with each other, although the correlation coefficient was from 0.31 (office SBP versus 24-hour SBP) to 0.45 (office DBP versus home DBP). Office, home, average 24-hour, and daytime SBP as well as DBP were significantly lower in the Mg period than the control period. Average differences in SBP assessed by the 3 methods were 2 to 4 mm Hg, and those in DBP were 1 to 2 mm Hg. Changes in nighttime SBP and DBP were comparable to those in daytime BP, although the changes in nighttime BP were not statistically significant.

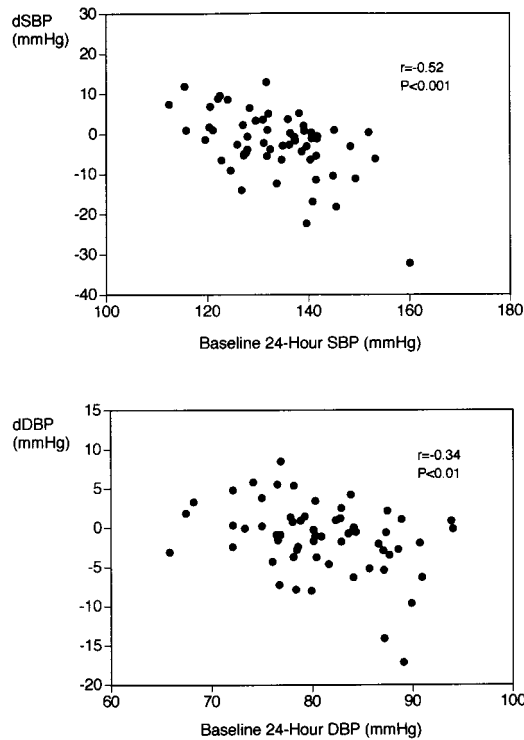
Levels of electrolyte and BP in men and women are shown in Table 4. Baseline serum Mg was lower and urinary Mg was higher in men than in women, although these differences

were not significant. Office, home, and 24-hour BPs decreased significantly with Mg supplementation in men, but these changes were not significant in women.

The Figure shows the relationship between changes in 24-hour BP with Mg supplementation and levels of 24-hour BP in the control period. The changes in both SBP and DBP correlated negatively with their baseline levels. The changes in 24-hour BP also correlated negatively with changes in serum Mg level (Table 5). Correlations between changes in 24-hour BP and age, control levels of serum Mg, control levels or changes in urinary Mg, or control levels of urinary Na were not significant.

Table 6 shows results of subgroup analysis regarding the changes in 24-hour BP with Mg supplementation. Age, gender, antihypertensive medication, drinking habit, and the order of the control and Mg periods did not significantly influence the changes in 24-hour BP, although the Mg-induced BP reduction tended to be greater in older subjects, men, and subjects taking antihypertensive medication. Subjects with high (above average) 24-hour SBP in the control period showed significantly greater reduction in 24-hour SBP (-5.3 ± 1.5 mm Hg) than those with low 24-hour SBP. Similarly, subjects with high 24-hour DBP showed greater reduction of 24-hour DBP (-2.7 ± 0.9 mm Hg) with Mg supplementation than those with low 24-hour DBP.

In multiple regression analysis, the baseline level of 24-hour SBP was an independent determinant for the change



Relationship between 24-hour BP in the control period and changes in 24-hour BP with Mg supplementation. dSBP indicates change in 24-hour SBP; dDBP, change in 24-hour DBP.

in 24-hour SBP with Mg supplementation. The baseline 24-hour DBP was a significant determinant for the change in 24-hour DBP. Other variables were not significant determinants for the change in 24-hour SBP or DBP.

Discussion

In the present study, supplementation with Mg for 8 weeks significantly lowered BP, with increases in serum Mg concentration and urinary Mg excretion in hypertensive patients. The reduction in BP was detected by 3 different methods, ie, measurement of casual office BP, self-measurement of home BP, and 24-hour ambulatory BP monitoring. Our results provide additional support for the antihypertensive effect of high dietary Mg intake, although the reduction in BP may be small.

Dietary Mg intake appears to be declining in developed countries.⁴ In the United States, it was estimated to be 475 to 500 mg/d at the turn of the century,²³ but it was 283 mg/d for men and 215 mg/d for women in 1989 to 1990.²⁴ In Japan, estimated Mg intake in 1980 was 240 mg/d.²⁵ The recent recommended daily allowances for Mg for adults are 280 mg for women and 350 mg for men in the United States²⁶ and 4 mg/kg in Japan.²⁷ In earlier intervention studies, amounts of supplemental Mg were from 15 mmol (360 mg) to 40 mmol (960 mg) daily. A dose of 15 or 20 mmol was often used because higher doses may cause adverse effects such as diarrhea. In the present study, 20 mmol/d (480 mg) Mg was given to the study subjects, most of whom completed the protocol without adverse symptoms. This dose is considered to be within the upper range of physiological intake, although it may increase average Mg intake by about 200%.

TABLE 5. Correlations Between Changes in 24-Hour BP With Mg Supplementation and Age, Baseline BP, Serum and Urinary Mg, and Urinary Na Excretion

Parameter	Change in 24-h SBP		Change in 24-h DBP	
	r	P	r	P
Age	-0.187	0.153	-0.196	0.133
Control 24-h SBP	-0.523	<0.001	-0.343	0.007
Control SMg	0.198	0.129	0.221	0.090
Change in SMg	-0.324	0.011	-0.337	0.008
Control UMg	0.093	0.483	0.003	0.982
Change in UMg	-0.091	0.491	-0.089	0.502
Control UNa	-0.137	0.298	-0.190	0.147

SMg indicates serum Mg; UMg, urinary magnesium; and UNa, urinary sodium.

Urinary Mg excretion in the control period was approximately 3 mmol/d in the present study. This level is similar to that observed in US studies^{28,29} but was lower than that seen in European studies^{10,30} or observational studies in China and Cameroon.^{31,32} These differences may be attributed to different lifestyles among populations. Individual level of serum Mg in the control period was within the normal range, except in a few patients whose level was slightly low. Therefore, the study subjects did not seem to have severe Mg deficiency. It has been shown that measurements of serum ionized Mg taken using ion-selective electrodes and erythrocyte-free Mg²⁺ by ³¹P NMR provide more precise estimation of body Mg status than conventional measurement of serum Mg.⁷

TABLE 6. Changes in 24-Hour BP With Mg Supplementation: Subgroup Analysis

Parameter	24-h SBP, mm Hg	24-h DBP, mm Hg
Age, y		
≥60	-4.1±2.0	-2.5±1.0
<60	-1.1±0.9	-0.4±0.6
Gender		
Men	-3.7±1.6	-2.1±0.9
Women	-0.8±1.1	-0.4±0.6
Medication		
Yes	-3.6±1.3	-1.9±0.7
No	-0.4±1.7	-0.4±1.0
Drinking habit		
Yes	-2.5±1.6	-1.5±1.0
No	-2.5±1.4	-1.2±0.7
Order		
Control-Mg	-2.9±1.5	-1.9±0.8
Mg-Control	-2.0±1.4	-0.8±0.8
Control 24-h BP		
High	-5.3±1.5†	-2.7±0.9*
Low	0.4±1.3	-0.2±0.7

Medication indicates antihypertensive medication; High, SBP ≥134 mm Hg (n=30) and DBP ≥81 mm Hg (n=27); Low, SBP <134 mm Hg (n=30) and DBP <81 mm Hg (n=33).

*P<0.05, †P<0.01 between subgroups.

Unfortunately, we did not determine serum ionized Mg or intracellular free Mg²⁺ in the present study.

Results of Mg supplementation studies based on casual BP measurement have been inconsistent.³³ Significant reduction in BP was reported in several studies^{10–12,28} but not in others.^{13,14,29,30} Lind et al³⁴ observed that Mg supplementation had no general effects on BP, but it lowered BP in subgroups with low urinary Mg excretion. Average changes in BP produced by Mg supplementation were -12 to -3 mm Hg for SBP and -8 to -3 mm Hg for DBP in positive studies. They were -7 to $+3$ mm Hg and -7 to $+1$ mm Hg, respectively, in negative studies. Doses of supplemental Mg were 20 to 40 mmol/d in the positive studies, except 1 study (15 mmol) in patients receiving diuretic treatment,¹⁰ while they were 15 to 20 mmol in the negative studies. The study subjects had mild to moderate hypertension in most trials, but some negative studies included subjects with high normal BP.^{12,30} In our study, casual office BP decreased by 3.7/1.7 mm Hg on average after Mg supplementation at a dose of 20 mmol/d for 8 weeks in hypertensive patients. These findings taken together, Mg supplementation appears to lower BP at least in some hypertensive subjects, although its antihypertensive effect may be small. Subjects with Mg-depleted status caused by low dietary intake or diuretic use may respond to oral Mg intake with greater BP reductions.

In our study, small but significant reductions in BP were also revealed by repeated home BP measurement and 24-hour ambulatory BP monitoring. These methods are considered to be more reliable for the assessment of pharmacological and nonpharmacological treatments of hypertension compared with casual BP measurement, which may overestimate or underestimate the effects of treatment because of several factors such as poor reproducibility, observer bias, white-coat phenomenon, and placebo effects.^{17,21} In the present study, the average reduction in 24-hour BP was 2.5/1.4 mm Hg, and changes in daytime and nighttime BPs were comparable. Our results are consistent with a report by Haga,²⁰ who examined effects of Mg supplementation (25 mmol/d for 2 weeks) on 24-hour BP in a small number of hypertensive patients. In the present study, we examined the effects of Mg supplementation on home BP and showed small but significant reductions (2.0/1.4 mm Hg on average). Our results also support the usefulness of home and ambulatory BP monitoring, since these methods detected changes in BP of <2 mm Hg in a moderate number of study subjects.

Several mechanisms may be involved in the antihypertensive effect of Mg. Mg ions lower resting levels of intracellular Ca²⁺ by competing with Ca²⁺ for membrane-binding sites and modulating Ca binding and release from the sarcoplasmic reticulum.¹ Thus, it can induce vasodilation as an intracellular Ca blocker. At the cell membrane, Mg²⁺ regulates ion flux through voltage-gated, acetylcholine-activated, Ca²⁺-activated, and ATP-activated K⁺ channels. These actions may also be involved in the cardiovascular effects of Mg²⁺. Cardiac and vascular smooth muscle cells are vulnerable to deficits in extracellular Mg²⁺, and the deficits in Mg²⁺ result in elevation of intracellular Ca²⁺ in these cells.¹

It has been shown that hypertensive patients have reduced serum and intracellular levels of Mg compared with normo-

tensive subjects.^{5,6} In addition to the low Mg intake, various factors such as high salt intake and use of alcohol and thiazide diuretics may also cause the Mg-deficient status by promoting renal Mg excretion.¹ The BP-lowering effect of Mg supplementation was apparent in subjects with low urinary Mg excretion³⁴ and in subjects receiving long-term diuretic treatment.¹⁰ In the present study, relationships between control levels of serum or urinary Mg and changes in 24-hour BP were not significant, but changes in serum Mg were correlated inversely with the changes in 24-hour BP. Our findings suggest that the actual increase in body Mg is more strongly related to the antihypertensive effect of Mg supplementation than the baseline level of serum or urinary Mg. The changes in 24-hour BP with Mg supplementation tended to be greater in treated than in untreated patients. However, this tendency did not seem to be due to diuretic use because thiazide diuretics were prescribed in only 5 of 40 treated subjects and the changes in BP in these 5 subjects were not marked. Sodium and alcohol intakes did not significantly affect the Mg-induced BP reduction in our study. The absence of severe Mg deficiency in the study subjects may account for the only slight reductions in BP with Mg supplementation and lack of clear association between baseline Mg status and the changes in BP.

The reductions in 24-hour BP with Mg supplementation were correlated with baseline levels of BP in the present study. The ambulatory BP decreased by 5.3/2.7 mm Hg in subjects with higher than average baseline BP, whereas it did not change in those with low baseline BP. Our results were consistent with an earlier study in which Mg supplementation lowered BP in hypertensive patients but not in normotensive subjects.²⁰ Although the precise mechanisms responsible for the different BP responses to Mg supplementation were not clarified, antihypertensive drugs including Ca antagonists are known to be more effective in patients with higher BP and have little effect on normotensive subjects. Our study suggests that the BP-lowering effect of high Mg intake is enhanced with elevation of baseline BP.

The antihypertensive effect of Mg supplementation was evident in men but not in women in our study. It also tended to be greater in older subjects than in younger subjects. Gender and age are possible determinants of BP response to mineral intake, as shown in the case of dietary Na.³⁵ However, the influence of gender and age were not significant in multiple regression analysis.

In summary, oral Mg supplementation significantly decreased office, home, and 24-hour BPs in hypertensive patients, and this effect was greater in subjects with higher baseline BP. Our study supports the usefulness of increasing dietary Mg intake as a part of lifestyle modifications in the management of hypertension. However, the therapeutic value of high Mg intake may be limited because its antihypertensive effect appears to be small.

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