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Additional antihypertensive effect of magnesium supplementation with an angiotensin II receptor blocker in hypomagnesemic rats

Kyubok Jin[1], Tae Hee Kim[2], Yeong Hoon Kim[2], and Yang Wook Kim[1]

[1]Department of Internal Medicine, Inje University Haeundae Paik Hospital, Busan; [2]Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, Korea

Background/Aims: Magnesium (Mg) is an essential element for vascular function and blood pressure regulation. Several studies have demonstrated that Mg concentration is inversely associated with blood pressure, and that Mg supplementation attenuates hypertension. The purpose of this study was to evaluate the effect of dietary Mg supplementation on the blood pressure effects of an angiotensin II receptor blocker (ARB) in hypomagnesemic rats.
Methods: Fifty male Sprague-Dawley rats were randomly divided into Mg-deficient (n = 30), normal diet plus Mg (n = 10), and control groups (n = 10). Mg-free, high-Mg, and normal-Mg diets were respectively fed to the rats. After 14 weeks, 10 of the 30 Mg-deficient rats were treated with Mg, 10 Mg-deficient rats received an ARB, and 10 Mg-deficient rats received an ARB plus Mg for 4 weeks.
Results: Systolic blood pressure was significantly higher in the Mg-deficient rats than in the control rats at week 14. Hypomagnesemic rats exhibited decreased systolic blood pressure after treatment with Mg, and systolic blood pressure showed a greater decrease after ARB treatment. Treatment with the ARB/Mg combination resulted in the greatest decrease in systolic blood pressure. Mg deficiency did not affect the serum angiotensin II level, but did increase the serum aldosterone concentration. Concomitant Mg/ARB supplementation significantly decreased the elevated serum aldosterone level in hypomagnesemic rats. Kidney tissues of the hypomagnesemic rats revealed mild to moderate inflammatory infiltrates. Mg and/or ARB treatment did not reverse the inflammatory reaction in the kidneys of hypomagnesemic rats.
Conclusions: Concurrent dietary Mg supplementation can enhance ARB-induced blood pressure reduction in rats with hypomagnesemic hypertension.

Keywords: Magnesium; Hypertension; Angiotensin receptor antagonists

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Correspondence to
Yang Wook Kim, M.D.
Department of Internal Medicine, Inje University Haeundae Paik Hospital, 875 Haeun-daero, Haeundae-gu, Busan 612-862, Korea
Tel: +82-51-797-0603
Fax: +82-51-797-3282
E-mail: kyw8625@chol.com

INTRODUCTION

Magnesium (Mg) is the second most abundant intracellular cation in the body. Studies have demonstrated that Mg deficiency enhances reactivity of arteries to vasoconstrictors, promotes vasoconstriction, and increases peripheral resistance, leading to increased blood pressure [1-3]. In contrast, Mg supplementation is associated with a significant decrease in blood pressure [4,5]. Mg deficiency is related to vascular structural and functional changes such as media thickening, increased media-to-lumen ratio, and increased contraction, which are characteristic *in vitro* and *in vivo* vascular changes [6,7]. Furthermore, Mg deficiency is

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associated with inflammation, oxidative stress, and endothelial dysfunction [8-10]. In experimental models of hypertension, the intracellular free Mg^{2+} concentration was negatively correlated with blood pressure, while the intracellular free Ca^{2+} concentration was positively correlated with blood pressure; and these concentrations were inversely associated [11,12]. These findings suggest that Mg may compete with calcium in blood pressure regulation.

Although many clinical and experimental studies support a critical role for Mg in the development of hypertension, the therapeutic value of Mg in the treatment of hypertension has not been established [13,14]. Dietary Mg supplementation during prehypertension and hypertension development in spontaneously hypertensive rats prevented a rise in blood pressure [15,16], suggesting a Mg-dependent physiological mechanism of blood pressure regulation [17]. Few studies have investigated the effects of Mg deficiency on the hormonal systems that control blood pressure. Angiotensin II decreases intracellular Mg in a dose-dependent manner, and this effect is inhibited by angiotensin II receptor blockers (ARBs) [18]. Mg deficiency may promote an angiotensin II-induced rise in blood pressure, aldosterone concentration, and vasoconstrictive prostaglandins [19].

The aim of this study was to evaluate the effect of dietary Mg supplementation on the blood pressure effects of an ARB in hypomagnesemic rats.

METHODS

Animals

Fifty male Sprague-Dawley rats (6 weeks old; average body weight, 180 g; Orient Bio, Seoul, Korea) were used in this study. The animals were housed in a climate-controlled vivarium with 12-hour light-dark cycle and were fed diet and water *ad libitum*. All animal experiments were conducted according to the guidelines formulated by the Inje University Animal Care and Use Committee (Busan, Korea).

Experimental procedures

The rats were randomly divided into control diet (#114551, Dyets Inc., Bethlehem, PA, USA) (n = 10), control diet with Mg treatment (n = 10), and Mg-free diet groups (n = 30). The Mg oxide composition of the control diet was 26.53 g/kg. After 14 weeks, the rats in the Mg-free diet group were randomly assigned to Mg treatment (n = 10), ARB treatment (n = 10), and Mg and ARB treatment subgroups (n = 10). For 4 weeks, the Mg treatment group received Mg (3,200 mg/kg/day) dissolved in food, the ARB treatment group was intraperitoneally administered losartan (30 mg/kg/day), and the Mg and ARB treatment group was given Mg (3,200 mg/kg/day) and losartan (30 mg/kg/day) as in the other two groups. After 4 weeks, blood pressure was determined by tail plethysmography (IITC Life Science, Woodland Hills, CA, USA). Conscious rats were placed in a restrainer on a warming pad and allowed to rest in a cage for 15 minutes before blood pressure measurement. Rat tails were placed inside a tail cuff, and the cuff was inflated and released several times to condition the animal to the procedure.

At the end of the experiment, the rats were anesthetized with sodium pentobarbital (50 mg/kg, intraperitoneal) and euthanized by exsanguination using cardiac puncture. The kidneys were removed and weighed. A piece of the kidney was separated and fixed in 10% formalin for histological examination, and another piece was processed as described below. The remaining tissue was cleaned with phosphate-buffered saline, snap-frozen in liquid nitrogen, and stored at -70°C until processed.

Values of serum Mg (Integra 800, Roche, Indianapolis, IN, USA), potassium (ADVIA 2400, Roche), calcium (ADVIA 2400, Siemens, Mannheim, Germany), angiotensin II, and aldosterone (Phoenix Pharmaceuticals, Burlingame, CA, USA) were analyzed using the appropriate specific procedures.

Histology

For light microscopy studies, the formalin-fixed kidney tissues were stained with hematoxylin and eosin, and Masson's trichrome by standard methods. Interstitial inflammation, fibrosis, and tubular atrophy were graded by the renal pathology study group of the Korean Society of Pathologists according to the following grading system: negative (≤ 10%), mild (11% to 25%), moderate (26% to 50%), and severe (> 50%) [20].

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Statistical analysis

Analysis of variance and a post hoc Tukey test (SPSS Inc., Chicago, IL, USA) were used for statistical evaluation of the data, which are presented as means ± SD. Values of $p \leq 0.05$ indicated significance.

RESULTS

Blood pressure effects of Mg and/or ARB treatments in Mg-deficient rats

Systolic blood pressure was similar between the control group and the Mg-free diet group (Mg-deficient rats) during the first 5 to 10 weeks. At week 14, systolic blood pressure was significantly higher in the Mg-deficient rats than in the control rats ($p = 0.034$) (Fig. 1A). Systolic blood pressure decreased during treatment with Mg and/or ARB in the hypomagnesemic rats. Each Mg/ARB treatment resulted in a similar reduction in systolic blood pressure. The decrease in systolic blood pressure was significantly greater ($p < 0.028$) in the Mg/ARB treatment group (44.3% ± 6.9% decrease) than in the Mg-only (28.7% ± 5.6% decrease) or ARB-only (28.9% ± 4.8% decrease) treatment group (Fig. 1B and 1C). These findings suggest that long-term hypomagnesemia induces hypertension and that concurrent dietary Mg supplementation enhances ARB-induced blood pressure reduction in hypomagnesemic rats.

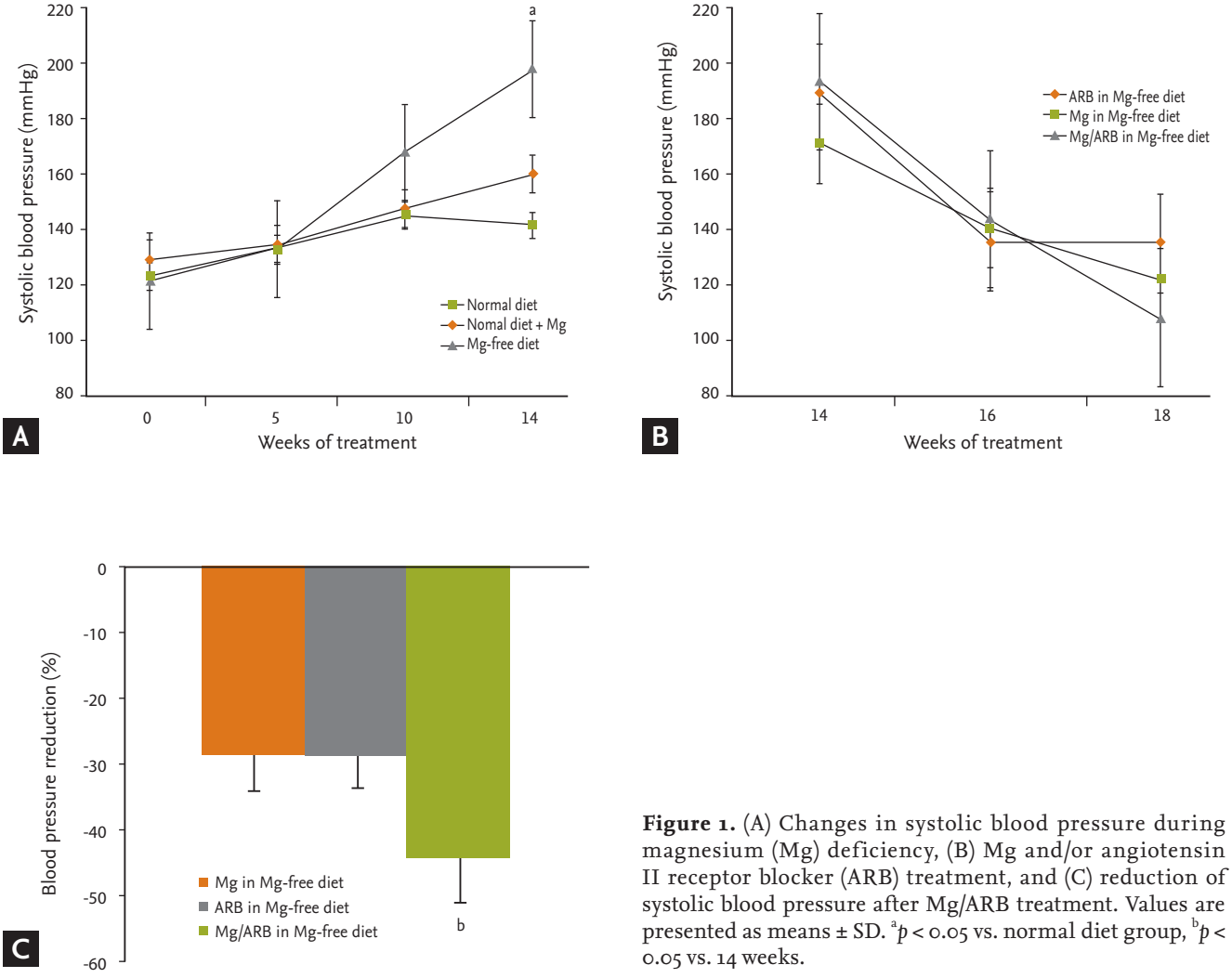

Figure 1. (A) Changes in systolic blood pressure during magnesium (Mg) deficiency, (B) Mg and/or angiotensin II receptor blocker (ARB) treatment, and (C) reduction of systolic blood pressure after Mg/ARB treatment. Values are presented as means ± SD. [a]$p < 0.05$ vs. normal diet group, [b]$p < 0.05$ vs. 14 weeks.

Effects of the Mg-free diet and Mg and/or ARB treatment on biochemical parameters

As shown in Table 1, serum calcium and potassium levels were similar among the study groups at weeks 14 and 18. Fig. 2 presents the serum levels of angiotensin II and aldosterone in the rats. The serum angiotensin II level did not differ among the groups during the study period. However, the serum aldosterone level

Table 1. Serum biochemical parameters in each diet group during induction of hypomagnesemia and treatment of hypomagnesemic rats

Hypomagnesemia induction period	Baseline			14 wk		
	Normal diet	Normal diet + Mg	Mg-free diet	Normal diet	Normal diet + Mg	Mg-free diet
Mg, mg/dL	1.63 ± 0.43	1.82 ± 0.14	2.10 ± 0.30	4.60 ± 1.07[a]	7.52 ± 1.37[a]	1.84 ± 0.37[a]
Ca, mg/dL	9.60 ± 1.04	9.83 ± 0.41	9.97 ± 0.74	10.06±1.62	10.62 ± 0.69	9.54 ± 0.47
K, mmol/L	5.55 ± 1.06	4.99 ± 0.46	5.50 ± 0.59	5.60±0.20	5.05 ± 0.49	5.38 ± 0.49
Hypomagnesemic rat treatment period	**14 wk**			**18 wk**		
	Mg treatment	ARB treatment	Mg/ARB treatment	Mg treatment	ARB treatment	Mg/ARB treatment
Mg, mg/dL	1.97 ± 0.16	1.81 ± 0.18	1.75 ± 0.13	4.18 ± 0.28[b]	1.59 ± 0.49	3.60 ± 0.20[b]
Ca, mg/dL	9.55 ± 0.73	9.80 ± 0.69	9.28 ± 0.48	10.91 ± 0.48	10.74 ± 0.21	9.95 ± 0.39
K, mmol/L	5.27 ± 0.44	5.67 ± 0.93	5.21 ± 0.55	5.18 ± 0.22	5.77 ± 0.34	5.97 ± 0.25

Values are presented as means ± SD.
[a]$p < 0.05$ vs. baseline.
[b]$p < 0.05$ vs. 14 weeks.

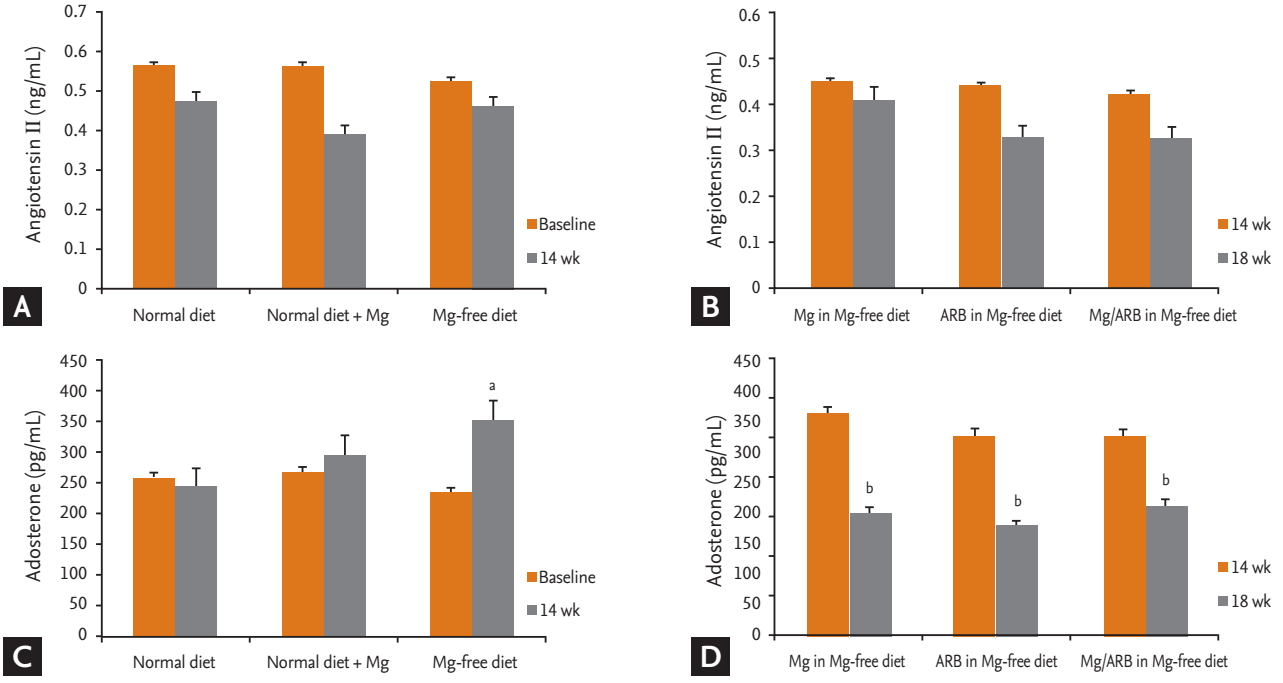

Figure 2. (A) Change in serum angiotensin II during magnesium (Mg) deficiency and (B) Mg and/or angiotensin II receptor blocker (ARB) treatment. (C) Change in aldosterone level during Mg deficiency and (D) Mg and/or ARB treatment. Values are presented as means ± SD. [a]$p < 0.05$ vs. other group, [b]$p < 0.05$ vs. 14 weeks.

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was significantly higher in the hypomagnesemic rats compared with the rats in the other two diet groups. Treatment with Mg and/or ARB tended to decrease the serum angiotensin II level in hypomagnesemic rats, but the difference was not significant. In contrast, Mg and/or ARB treatment resulted in a significant decrease in the elevated serum aldosterone level in hypomagnesemic rats. These findings suggest direct effects of Mg deficiency on aldosterone production, independent of the renin-angiotensin system.

Effects of the Mg-free diet and Mg and/or ARB treatment on renal pathology

The kidney tissues of the hypomagnesemic rats exhibited mild to moderate inflammatory infiltration of mononuclear leukocytes, interstitial fibrosis, tubular atrophy, and calcium deposits. Treatment with Mg and/or ARB did not reverse the inflammatory reaction in the kidneys of hypomagnesemic rats (Fig. 3).

DISCUSSION

Mg is an essential cation with crucial roles in many physiological functions. Mg may be physiologically important in blood pressure regulation, and changes in Mg levels may contribute to the pathoetiology of hypertension [17]. Many experimental and clinical studies support a key role for Mg deficiency in the pathogenesis of hypertension. Reports have demonstrated an inverse correlation between body Mg levels and blood pressure, as well as a hypotensive effect of dietary Mg supplementation [21-24]. Nevertheless, the therapeutic and preventive value of Mg supplementation for managing hypertension remains controversial. Some studies have documented blood pressure-lowering effects of Mg in essential and experimental hypertension [25-27], but other studies have not confirmed these findings [13,14,28]. Mg supplementation failed to significantly reduce blood pressure in mild to moderate hypertensive patients in some short-term studies, whereas long-term Mg supplementation had some beneficial antihypertensive effects, particularly in patients who are Mg deficient [29,30]. In recent clinical studies, oral Mg supplementation improved vascular functions in elderly patients with diabetes and improved borderline hypertension [31-35]. In the present study, we examined whether Mg supplementation, started after the establishment of hypertension, could influence the lowering of blood pressure and the progression of hormonal and renal histological changes in hypomagnesemic rats.

Long-term Mg deficiency in experimental animals potentiates responses to vasoconstrictor agents, attenuates responses to vasodilator agents, increases vascular tone, and elevates blood pressure [36,37]. Some of these effects may be attributable to endothelial dysfunction, vascular structural changes, vascular inflammation, and oxidative stress [7,38,39]. Hypomagnesemia can lead to enhanced intracellular calcium levels and calcium overload in blood vessels [40]. Mg may influence the production of certain vasoactive agents such as endothelin-1 [41] and prostacyclin [42]. Plasma endothelin-1 levels are elevated in hypomagnesemic rats, and the levels are reduced in Mg-supplemented rats [43]. Increased extracellular Mg levels induce endothelial release of prostacyclin [44]. These findings suggest that a direct effect of Mg deficiency on vascular smooth muscle may be involved in the elevation of vascular tone [17] and that Mg supplementation may have the effect of lowering blood pressure.

The present results confirmed that Mg deficiency is related to hypertension and that Mg supplementation in hypomagnesemic rats can attenuate high blood pressure. Serum angiotensin II levels remained unchanged in Mg-deficient rats, and Mg supplementation did not alter angiotensin II levels in hypomagnesemic rats. However, serum aldosterone levels increased in Mg-deficient rats, and Mg and/or ARB treatment significantly ameliorated these increased serum aldosterone levels. In a previous study, angiotensin II increased the concentration of cytosolic free calcium and sodium with a concomitant decrease in cytosolic free Mg^{2+} concentration, and these effects were inhibited by an ARB [18]. Our data show that serum aldosterone increased without a changed in angiotensin II in hypomagnesemic rats. This dissociation suggests that Mg may have a direct effect on aldosterone synthesis, rather than an indirect effect via the renin angiotensin aldosterone system. Additionally, a report has shown that decreased muscle potassium and increased sodium lead to Mg deficiency,

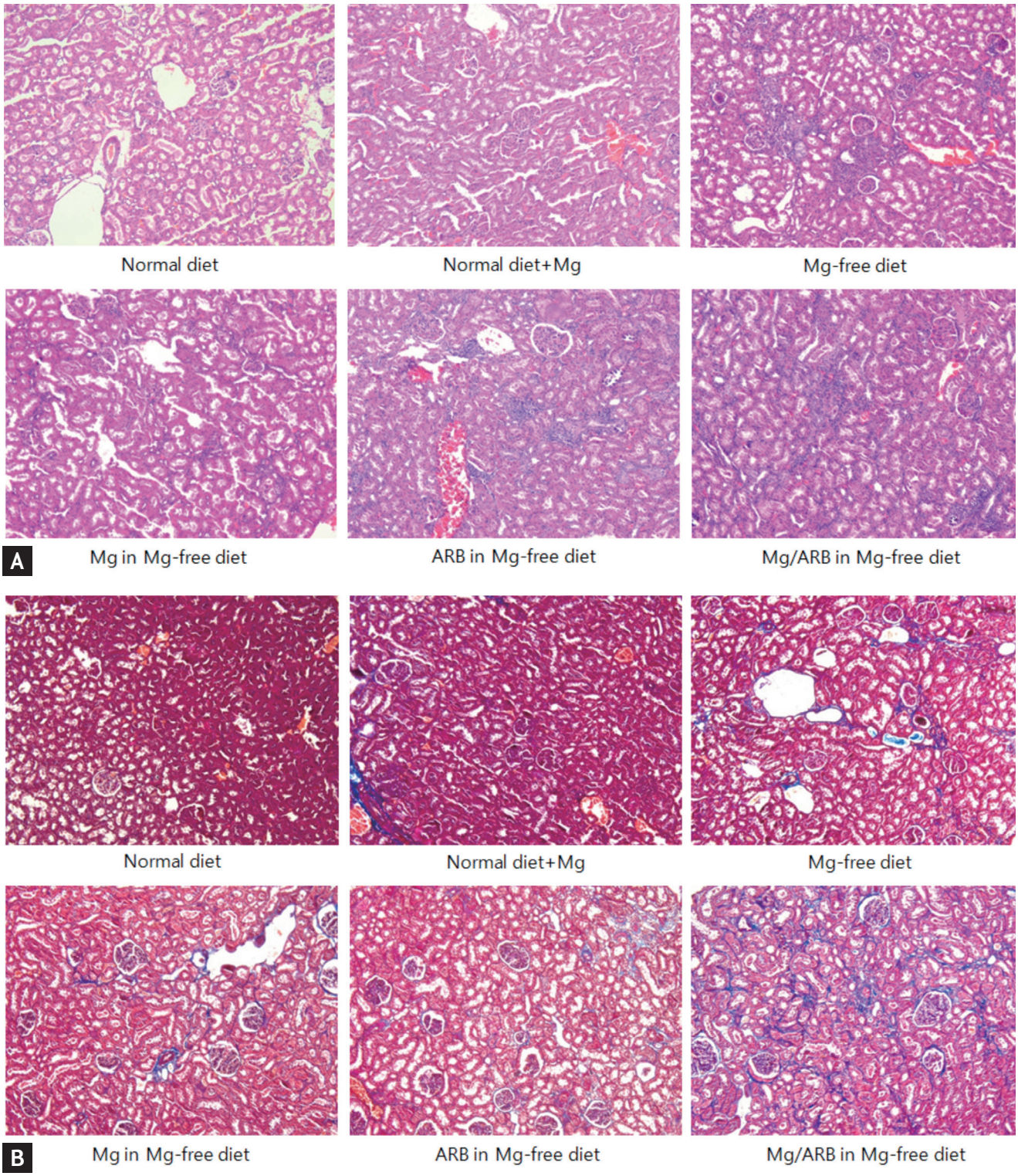

Figure 3. (A, B) Effects of magnesium (Mg)-deficient diet and Mg and/or angiotensin II receptor blocker (ARB) treatment on renal pathology (A, H&E, × 100; B, Masson's trichrome stain, × 100). Normal diet: inflammation (negative), fibrosis (negative), and tubular atrophy (negative). Normal diet + Mg: inflammation (negative), fibrosis (negative), and tubular atrophy (negative). Mg-free diet: inflammation (moderate), fibrosis (mild), and tubular atrophy (negative). Hypomagnesemic rats treated with Mg: inflammation (mild), fibrosis (negative), and tubular atrophy (negative). Hypomagnesemic rats treated with ARB: inflammation (moderate), fibrosis (mild), and tubular atrophy (negative). Hypomagnesemic rats treated with Mg/ARB: inflammation (moderate), fibrosis (moderate), and tubular atrophy (mild).

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indicating the possibility of increased aldosterone secretion [45]. The precise mechanism by which Mg deficiency stimulates aldosterone production is not known. These findings suggest that Mg^{2+} fluxes are under the control of various hormones such as insulin, endothelin-1, norepinephrine, epinephrine, aldosterone, and vasopressin [18].

Although the mechanism by which Mg treatment modulates vascular tone and reactivity is unclear, Mg^{2+}-associated changes in intracellular signaling pathways, altered cellular Mg^{2+}/Ca^{2+} interactions in vascular smooth muscle cells, and improved endothelial function may be important factors [46,47]. Mg can displace and compete with calcium, modulate intracellular calcium mobilization, and regulate calcium efflux [48]. We did not find a correlation between blood pressure and calcium levels because we did not measure the intracellular concentrations of Mg and calcium. Additionally, the duration of dietary Mg supplementation might have been too short in the present. Furthermore, the serum Mg level decreased significantly after 14 weeks of the Mg-free diet, suggesting that Mg cell turnover is not an acute phenomenon.

Studies investigating the effects of dietary Mg on blood pressure have reported contradictory results. Our data showing that Mg supplementation attenuated hypertension are in agreement with those of some studies, but differ from other studies reporting no blood pressure lowering effects of Mg supplementation [13,14]. These contradictory results may be related to differences in experimental factors, including diet composition, feeding protocol, rat strain, or definitions of hypertension. A physiological mechanism underlying blood pressure control may be dependent on the Mg status during a particular developmental stage. If so, the stage must lie between 6 and 14 weeks, the time during which blood pressure increases steeply in spontaneously hypertensive rats [16]. Our results support these suggestions, as we demonstrated that Mg deficiency significantly induced the development of hypertension after 14 weeks.

In the present study, kidney tissues of the hypomagnesemic rats revealed mild to moderate inflammatory infiltration, and dietary Mg supplementation did not change these histological findings, which were distinguishable among the treatment groups. The renal tissue changes in the hypomagnesemic rats probably reflected early renal damage associated with the late phase of established hypertension.

In conclusion, dietary Mg supplementation attenuated blood pressure in rats with hypomagnesemic hypertension and enhanced the antihypertensive effect of an ARB. Mg supplementation may affect aldosterone synthesis independent of the renin angiotensin aldosterone system. Our data suggest that Mg supplementation may be helpful for managing hypertension concomitant with hypomagnesemia.

KEY MESSAGE

1. Magnesium (Mg) is inversely associated with blood pressure and Mg supplementation attenuates hypertension.
2. Dietary Mg supplementation can attenuate the blood pressure in hypomagnesemic hypertension and enhance the antihypertensive effect.
3. Mg supplementation may be helpful in managing hypertension concomitant with hypomagnesemia.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

Acknowledgments

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