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# Magnesium in hypertension: mechanisms and clinical implications

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Hypertension is associated with increased risk of cardiovascular disease and death. Evidence suggests that  $Mg^{2+}$  depletion contributes to hypertension. It is estimated that 25% or more of the United States population experiences chronic, latent  $Mg^{2+}$  depletion. This review explores mechanisms by which  $Mg^{2+}$  influences blood pressure, modifying risk of hypertension and complicating its treatment. Mechanisms addressed include effects upon i) sympathetic tone, via the modulation of N-methyl-D-aspartate (NMDA) receptor and N-type  $Ca^{2+}$  channel activity, influencing catecholamine release from sympathetic nerve endings; ii) vascular tone, via alteration of L-type  $Ca^{2+}$  and endothelial nitric oxide synthase (eNOS) activity and prostacyclin release; iii) renal  $K^+$  handling, influencing systemic  $K^+$  balance and potentially indirectly influencing blood pressure; iv) aldosterone secretion from the adrenal cortex; and v) modulation of pro-hypertensive inflammatory processes in dendritic cells and macrophages, including activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome and stimulation of isolevuglandin (IsoLG) production. Discovery of these mechanisms has furthered our understanding of the pathogenesis of hypertension, with implications for treatment and has highlighted the role of  $Mg^{2+}$  balance in hypertension and cardiovascular disease.

## KEYWORDS

magnesium, hypertension, aldosterone, NLRP3 inflammasome, isolevuglandins (IsoLG)

## Introduction

Magnesium is an essential ion and is required for normal health, including the cardiovascular system (de Baaij et al., 2015). Numerous studies have explored the association between  $Mg^{2+}$  and blood pressure, and evidence suggests that  $Mg^{2+}$  depletion contributes to hypertension. This review will focus on the effect of  $Mg^{2+}$  on blood pressure and hypertension and will discuss different mechanisms by which  $Mg^{2+}$  influences blood pressure.

Hypertension is widely prevalent. In the United States, it affects 119.9 million adults - nearly half the population (United States Centers for Disease Control and Prevention, 2015). Hypertension increases the risk of cardiovascular disease and stroke (Fuchs and Whelton, 2020). In 2020, it was estimated that cardiovascular disease contributed to around 19,000,000 deaths globally (Tsao et al., 2022).

Systemic  $Mg^{2+}$  depletion is common. Reports estimate that 25% or more of the population of the United States experiences chronic, latent  $Mg^{2+}$  depletion (Lowenstein and Stanton, 1986; Rosanoff et al., 2022).  $Mg^{2+}$  depletion is under-appreciated clinically, partly because reference ranges for plasma  $Mg^{2+}$  in clinical laboratories are based upon population distribution rather than healthy levels. Study groups in the United States

(Costello et al., 2016) and in Germany (Micke et al., 2021), have independently recommended an evidence-based lower limit of normal for serum  $Mg^{2+}$  of 2.07 mg/dL (0.85 mmol/L). However, a 2022 study found that in 41 out of 43 medical centers in 16 countries employ a lower limit beneath this recommended threshold (Rosanoff et al., 2022). Prevalence of  $Mg^{2+}$  depletion appears even higher in individuals with hypertension, as intracellular  $Mg^{2+}$  levels are lower in hypertensive individuals than control individuals (Resnick et al., 1984; Touyz et al., 1992). Plasma  $Mg^{2+}$ , a less sensitive indicator of  $Mg^{2+}$  deficiency, was found to be lower in hypertensive individuals with elevated renin but not in other hypertensive individuals (Resnick et al., 1983).

Dietary  $Mg^{2+}$  insufficiency is a common contributor to systemic  $Mg^{2+}$  depletion. The United States estimated average requirement (EAR) for  $Mg^{2+}$  is 255 mg/day for women aged 19–30 years, increasing to 265 mg/day for women aged  $\geq 31$  years. For men aged 19–30 the EAR is 330 mg/day, increasing to 350 mg/day for men aged  $\geq 31$  years (Rosanoff et al., 2012). According to the United States National Health and Nutrition Examination Survey (NHANES) 2013–2016 report, this EAR was not met in nearly half (48%) of the U.S. population (USDA Agricultural Research Service, 2019).

Commonly prescribed medications also contribute to systemic  $Mg^{2+}$  depletion (Ray et al., 2023). Given the contribution of  $Mg^{2+}$  depletion to cardiovascular disease (Kolte et al., 2014); it is particularly concerning that treatment with a first-line therapy for hypertension, thiazide-type diuretics, promotes urinary  $Mg^{2+}$  wasting and systemic  $Mg^{2+}$  depletion (Hollifield, 1986).

## Evidence for a relationship between $Mg^{2+}$ and hypertension

The earliest findings of an effect of  $Mg^{2+}$  upon blood pressure were reported more than 100 years ago, when Kenneth Blackfan (subsequently famous for his description of Diamond Blackfan anemia) and Charles McKhann described “a rapid fall in blood pressure” in children with glomerulonephritis and severely elevated blood pressure (Blackfan and Mills, 1923; Blackfan and McKhann, 1931). Studies much later would seek to understand the circumstances under which  $Mg^{2+}$  can attenuate hypertension.

Several studies have explored the relationship between dietary  $Mg^{2+}$  and blood pressure in experimental animals, with mixed results. In rats, some studies show increased blood pressure with dietary  $Mg^{2+}$  restriction (Berthelot and Esposito, 1983; Altura et al., 1984; Laurant et al., 1999; Murasato et al., 1999; Carlin Schooley and Franz, 2002; Blache et al., 2006), others do not (Itokawa et al., 1974; Overlack et al., 1987; Lowney et al., 1988; Luthringer et al., 1988; Evans et al., 1989; Liu et al., 1994; Laurant et al., 1997; Tomiyasu et al., 1998). No doubt these discrepancies reflect differences in experimental details such as strains used, severity of dietary  $Mg^{2+}$  restriction, and duration. In mice, dietary  $Mg^{2+}$  deficiency was shown to stimulate salt-sensitive increase in blood pressure in DBA but not C57Bl/6J mice (Kumagai et al., 2021). However, in C57Bl/6J mice, a  $Mg^{2+}$ -restricted diet did increase blood pressure raising-effects of sympathetic stimulation. In mice of the sv129 background, dietary  $Mg^{2+}$  restriction increased blood

pressure by 21 days until sacrifice at 5 weeks (Pitzer Mutchler et al., 2023). Intravenous  $Mg^{2+}$  infusion in rats attenuates increases in blood pressure resulting from angiotensin II (Atarashi et al., 1990) or sympathetic nerve stimulation (Shimosawa et al., 2004).

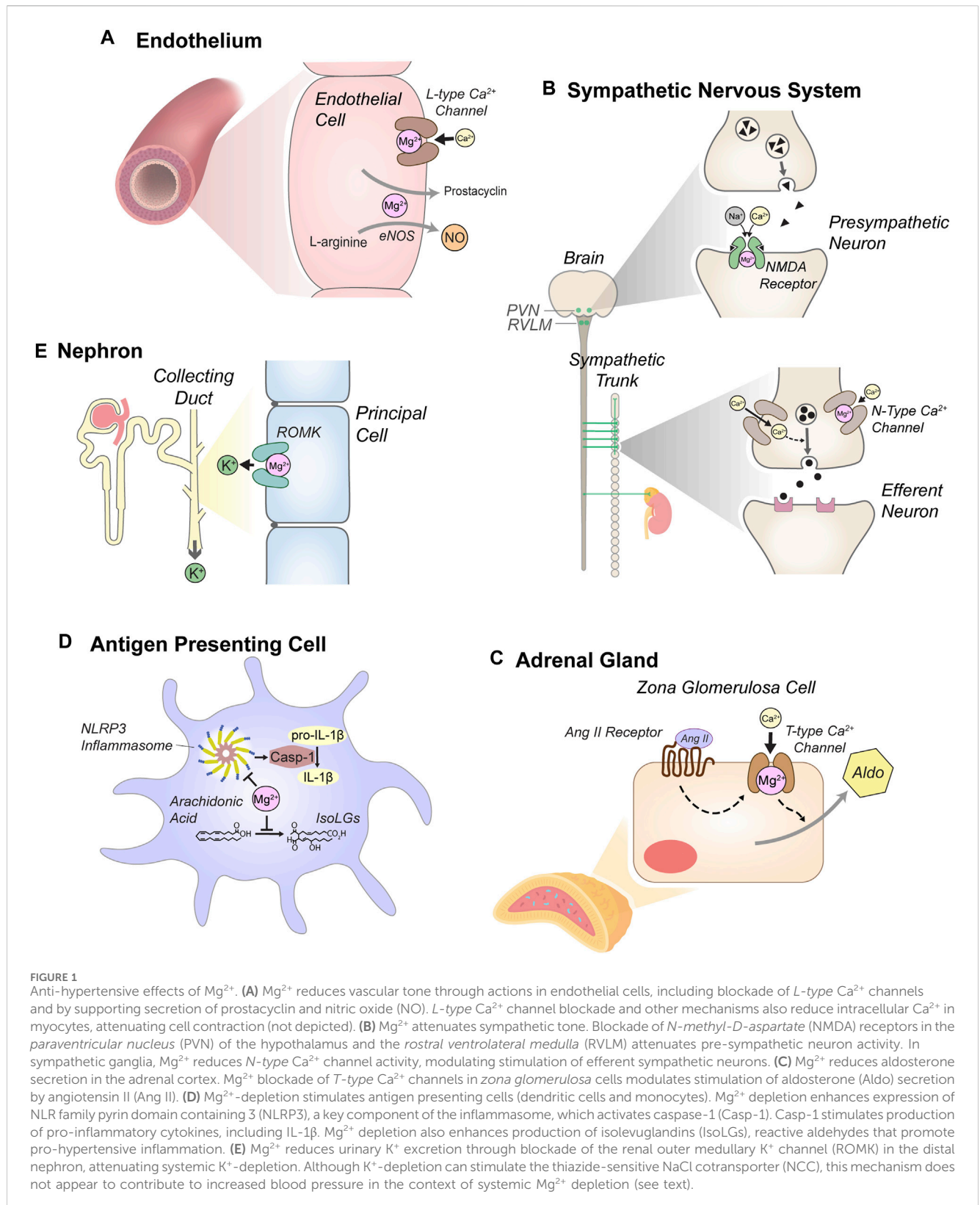
Observational studies have explored the correlation between circulating  $Mg^{2+}$  in humans and blood pressure. A structured review and subgroup analysis of observational studies explored the association between dietary  $Mg^{2+}$  intake and blood pressure. Findings suggested an inverse relationship between dietary  $Mg^{2+}$  intake and blood pressure, though heterogeneity in study methods complicated interpretation (Mizushima et al., 1998). In an observational study of 1,000 ambulatory hypertensive patients, hypomagnesemia was associated with worsened hypertension, as indicated by a greater number of prescribed anti-hypertensive medications (Whang et al., 1982). Plasma  $Mg^{2+}$  levels are lower in individuals with untreated elevated systolic blood pressure and diastolic blood pressure than in normotensive controls (Rodríguez-Moran and Guerrero-Romero, 2014; Rodríguez-Ramírez et al., 2015).

Numerous human clinical trials have examined the effects of  $Mg^{2+}$  supplementation in management of hypertension. A meta-analysis by Zhang et al., pooled 24 randomized controlled trials (RCTs) with a total of 2,028 participants. They concluded that supplementation of  $Mg^{2+}$  at a mean dose of 368 mg/day for a median period of 3 months resulted in 2 mmHg reduction in SBP (95% CI, 0.43–3.58 mmHg;  $p = 0.01$ ) and 1.78 mmHg reduction in DBP (CI, 0.73–2.82 mmHg;  $p = 0.001$ ) (Zhang et al., 2016). Another meta-analysis by Dibaba et al., reviewed 11 RCTs, including 543 participants.  $Mg^{2+}$  supplementation of 365–450 mg/day for a mean of 3.6 months significantly reduced SBP by a mean of 4.18 mmHg (standard mean difference:  $-0.20$ ; 95% CI:  $-0.37$ ,  $-0.03$ ) and DBP by a mean of 2.27 mmHg (standard mean difference:  $-0.27$ ; 95% CI:  $-0.52$ ,  $-0.03$ ) (Dibaba et al., 2017). Rosanoff et al., conducted a meta-analysis of 49 clinical trials that stratified study participants into the following groups: 1) untreated hypertensives 2) uncontrolled hypertensives 3) controlled hypertensives 4) normotensive subjects. They found that a  $Mg^{2+}$  dose of  $\geq 240$  mg/day decreases BP in treated but uncontrolled hypertensive individuals, and a dose of  $>600$  mg/day lowers BP in untreated hypertensives. There was no change in BP in individuals who were normotensive, had controlled HTN, or were  $Mg^{2+}$ -replete (Rosanoff et al., 2021). A meta-analysis of seven RCTs examining hypertensive individuals with diabetes found that  $Mg^{2+}$  supplementation reduced systolic blood pressure by 5.78 and diastolic blood pressure by 2.5 mmHg (Asbaghi et al., 2021). This is of particular interest, as diabetic patients tend to be  $Mg^{2+}$  depleted (Ray et al., 2023).

Together, these findings suggest that systemic  $Mg^{2+}$  depletion promotes increased blood pressure in patients with hypertension.

## Mechanisms influencing blood pressure

Because of its vast physiologic effects,  $Mg^{2+}$  depletion likely influences blood pressure via multiple mechanisms, as discussed below and summarized in Figure 1.



## Vascular tone

Effects of  $Mg^{2+}$  on vascular tone may contribute to its influence upon blood pressure. Empiric evidence for an effect of  $Mg^{2+}$  upon

vascular tone is demonstrated by the observations that decreased extracellular  $Mg^{2+}$  or systemic  $Mg^{2+}$  depletion in animals produces vasospasm and reduces microvascular blood flow (Altura and Turlapaty, 1982; Altura et al., 1983; Altura et al., 1984). Humans

given an acute  $\text{MgSO}_4$  infusion exhibit increased renal blood flow, despite reduced blood pressure (Nadler et al., 1987).

Vascular smooth muscle constriction is stimulated when  $\text{Ca}^{2+}$  enters smooth muscle cytosol via L-type voltage-gated  $\text{Ca}^{2+}$  channels. Intracellular  $\text{Ca}^{2+}$  stimulates phospholipase C and production of diacylglycerol (DG) and inositol 1,4,5-trisphosphate ( $\text{IP}_3$ ).  $\text{IP}_3$  activates the  $\text{IP}_3$  receptor, releasing  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum. Cytosolic  $\text{Ca}^{2+}$  then binds to calmodulin, activating myosin light chain kinase (MLCK). Activated MLCK phosphorylates the myosin light chain, stimulating interaction of actin and myosin, and eliciting cell contraction (Webb, 2003).

Intracellular  $\text{Mg}^{2+}$  attenuates myocyte contraction via several mechanisms.  $\text{Mg}^{2+}$  diminishes cellular  $\text{Ca}^{2+}$  entry via L-type voltage-gated  $\text{Ca}^{2+}$  channels (Zhang et al., 2007; Sharma et al., 2012). Intracellular  $\text{Mg}^{2+}$  inhibits  $\text{Ca}^{2+}$ -stimulated  $\text{Ca}^{2+}$ -release from the sarcoplasmic reticulum, at least in cardiac muscle (Dunnett and Nayler, 1978). The sarcoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase, which is required to return released  $\text{Ca}^{2+}$  to intracellular stores, requires  $\text{Mg}^{2+}$  for activity (Hasselbach et al., 1981). Consequently, low  $\text{Mg}^{2+}$  conditions prolong elevation of intracellular  $\text{Ca}^{2+}$  following release from intracellular stores (Gasallaherraiz et al., 1995). Thus,  $\text{Mg}^{2+}$  reduces smooth muscle contraction.

**Prostacyclin release:** Effects of systemic  $\text{Mg}^{2+}$  status upon vascular tone may be mediated, in part, by effects on prostacyclin release. Prostacyclin ( $\text{PGI}_2$ ) is recognized to have important systemic vasodilatory effects (Zhao and Richardson, 1990). In the kidney, prostacyclin is critical for maintaining vasodilation and blood flow in the context of extrarenal vasoconstriction. Mice lacking prostacyclin synthase exhibit hypertension, thickening of the aortic medial and adventitial layers, and nephrosclerosis (Yokoyama et al., 2002). In humans, a repeat polymorphism in the promoter region of the prostacyclin synthase gene was found to reduce prostacyclin synthase transcription and to be associated with increased odds of hypertension (Iwai et al., 1999).

$\text{Mg}^{2+}$  modulates vascular prostacyclin release. In cultured vascular endothelial cells or smooth muscle cells, increased extracellular  $\text{Mg}^{2+}$  stimulated prostacyclin secretion (Briel et al., 1987; Satake et al., 2004). In the rat deoxycorticosterone acetate (DOCA)-salt model of hypertension, a  $\text{Mg}^{2+}$ -enriched diet significantly increased  $\text{PGI}_2$  levels (Laurant et al., 1992). Infusion of  $\text{MgSO}_4$  into humans enhanced urinary excretion of immunoreactive 6-ketoprostaglandin  $\text{F}_{1\alpha}$  (6-keto- $\text{PGF}_{1\alpha}$ ), a stable break-down product of  $\text{PGI}_2$ , while reducing blood pressure (Nadler et al., 1987). The importance of prostaglandin synthesis in this blood pressure effect was demonstrated by the observation that cyclooxygenase inhibition prevented the decrease in blood pressure and increase in renal blood flow. Moreover, the  $\text{Mg}^{2+}$ -stimulated increase in  $\text{PGI}_2$  release was blocked by the calcium channel blocker, nifedipine, suggesting that the influence of  $\text{Mg}^{2+}$  on cyclooxygenase is dependent upon  $\text{Ca}^{2+}$  entry into cells.

**Nitric oxide metabolism:**  $\text{Mg}^{2+}$  also influences vascular tone through effects on nitric oxide (NO). Nitric oxide is an endogenous vasodilator produced in endothelial cells from L-arginine by endothelial NO synthase (eNOS) (Rees et al., 1989; Gamboa et al., 2007). In cultured endothelial cells, NO production was roughly 3-fold higher in cells grown in high (5 mM, or 12 mg/dL) than in control (1 mM, or 2.4 mg/dL) extracellular  $\text{Mg}^{2+}$  (Maier

et al., 2004). This finding was attributed to an observed increase in eNOS protein abundance in cells grown in high  $\text{Mg}^{2+}$ .

Altered NO release may contribute to effects of  $\text{Mg}^{2+}$  upon NO signaling. In mouse aorta and mesenteric vessels, endothelium-dependent,  $\text{Mg}^{2+}$ -induced arterial relaxation is attenuated by blockade of eNOS activity with N (gamma)-nitro-L-arginine methyl ester (L-NAME) (Kudryavtseva et al., 2024). In canine coronary arteries,  $\text{Mg}^{2+}$ -free conditions attenuated acetylcholine and ADP-stimulated, NO-dependent reduction in arterial tone (Pearson et al., 1998). The  $\text{Ca}^{2+}$  ionophore A23187, which induces endothelial NO release independently of receptor-mediated signaling mechanisms, reduced arterial tension in a  $\text{Mg}^{2+}$ -independent fashion. Bradykinin-stimulated vascular relaxation, which occurs via endothelium-dependent, but NO-independent mechanisms, was unaffected (Pearson et al., 1998). These findings suggest that  $\text{Mg}^{2+}$  is required for stimulation of NO release but not for NO-stimulated relaxation. Evidence that  $\text{Mg}^{2+}$  influences NO signaling in humans comes from a study examining flow-mediated vasodilation of the brachial artery (FMD), a process that is at least partly NO mediated (Green et al., 2014). Oral  $\text{Mg}^{2+}$  supplementation in individuals with coronary artery disease significantly improved FMD and exercise tolerance (Shechter et al., 2000).

$\text{Mg}^{2+}$  likely also promotes relaxation via additional, NO-independent pathways. Blockade of SK and IK  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels, which participate in endothelium-derived relaxation factor-stimulated arterial relaxation, blunted  $\text{Mg}^{2+}$ -dependent arterial relaxation additively with eNOS inhibition (Kudryavtseva et al., 2024).

Together, these observations suggest that systemic  $\text{Mg}^{2+}$  status could influence blood pressure through multiple effects on vascular tone.

## Sympathetic tone

$\text{Mg}^{2+}$  exerts an inhibitory effect on the sympathetic nervous system, whereas  $\text{Mg}^{2+}$  deficiency stimulates sympathetic tone.

Effects of  $\text{Mg}^{2+}$  upon the sympathetic nervous system are mediated, in part, through modulation of N-methyl-D-aspartate (NMDA) receptor activity. The NMDA receptor is a  $\text{Ca}^{2+}$ -selective ion channel that opens in response to NMDA and L-Glutamate (L-Glu) (Dingledine et al., 1999; Kagiya et al., 2001). NMDA receptor activity in the rostral ventrolateral medulla (RVLM) and hypothalamic paraventricular nucleus (PVN) increase sympathetic outflow and blood pressure (Dampney et al., 2003; Li and Pan, 2017). NMDA receptor activity is negatively regulated by  $\text{Mg}^{2+}$  (Dingledine et al., 1999). Thus, attenuation of NMDA receptor activity by  $\text{Mg}^{2+}$  may be expected to reduce blood pressure.

In support of this hypothesis, Kagiya et al., studied the effect of  $\text{Mg}^{2+}$  in the RVLM upon blood pressure. Injection of magnesium sulfate ( $\text{MgSO}_4$ ) into the RVLM exerted a dose-dependent attenuation of increased blood pressure occurring in response to NMDA injection (Kagiya et al., 2001).

$\text{Mg}^{2+}$  also negatively influences sympathetic tone through modulation of catecholamine release from peripheral nerve endings and by blocking N-type  $\text{Ca}^{2+}$  channels at nerve endings (Shimosawa et al., 2004). In neuronally differentiated PC12 cells,

N-type  $\text{Ca}^{2+}$  channel activity was decreased by elevated extracellular  $\text{Mg}^{2+}$  and increased by reduced extracellular  $\text{Mg}^{2+}$ . With cytosolic  $\text{Ca}^{2+}$  being a major stimulus for catecholamine release, low extracellular  $\text{Mg}^{2+}$  buffer enhanced norepinephrine release from the periarterial plexus of the mesenteric artery compared to control or high  $\text{Mg}^{2+}$  buffer. Urinary catecholamine excretion was found to be more than two-fold higher in  $\text{Mg}^{2+}$  deficient rats than control rats (Murasato et al., 1999).  $\text{Mg}^{2+}$  infusion also attenuated sympathetically mediated reflex tachycardia following hydralazine infusion (Shimosawa et al., 2004). In addition to reducing norepinephrine release from sympathetic neurons,  $\text{Mg}^{2+}$  also increased norepinephrine uptake in isolated adrenergic nerve granules, suggesting an influence upon norepinephrine reuptake in the synaptic cleft (von Euler and Lishajko, 1963; von Euler and Lishajko, 1973).

Effects of  $\text{Mg}^{2+}$  on the sympathetic nervous system have also been demonstrated in human subjects. James et al., studied the effect of  $\text{MgSO}_4$  infusion upon simulation of catecholamine release and blood pressure in response to endotracheal intubation. In controls, intubation rapidly increased circulating epinephrine levels, norepinephrine levels, and systolic blood pressure.  $\text{MgSO}_4$  infusion attenuated the increase in each of these (James et al., 1989).

Thus,  $\text{Mg}^{2+}$  modulates peripheral sympathetic nervous system activity, reducing blood pressure.

## Effects on $\text{K}^+$ and $\text{Na}^+$ handling

Systemic  $\text{Mg}^{2+}$  status could influence blood pressure indirectly, through effects on handling of  $\text{K}^+$  and  $\text{Na}^+$ .

Bodily  $\text{K}^+$  balance influences blood pressure. Several meta-analyses of clinical trials find that  $\text{K}^+$  supplementation reduces blood pressure in hypertensive individuals (van Bommel and Cleophas, 2012; Poorolajal et al., 2017; Filippini et al., 2020). The influence of  $\text{K}^+$  upon blood pressure is likely mediated by multiple mechanisms, including effects upon vascular tone and upon extracellular fluid volume. In Dahl salt-sensitive rats, a high  $\text{K}^+$ -diet promotes vascular relaxation (Raj et al., 1988). Fluid volume effects may occur secondary to enhanced tubular  $\text{Na}^+$  reabsorption in the context of systemic  $\text{K}^+$  depletion. In the kidney's proximal convoluted tubule (PCT), a low  $\text{K}^+$  diet enhanced protein abundance of the  $\text{Na}^+/\text{H}^+$  exchanger, type 3 (NHE3), promoting  $\text{Na}^+/\text{H}^+$  exchange (Shirley et al., 1990; Soleimani et al., 1990; Elkjær et al., 2002). In the distal convoluted tubule (DCT),  $\text{K}^+$  deficiency stimulates phosphorylation-mediated activation of sodium-chloride cotransporter (NCC) through modulation of the WNK/SPAK/OSR1 (with no lysine/SPS1-related proline-alanine-rich kinase/oxidative stress-responsive kinase 1) signal transduction pathway (Terker et al., 2015).

$\text{Mg}^{2+}$  depletion promotes  $\text{K}^+$  depletion. Because serum  $\text{K}^+$  represents only 2% of total body  $\text{K}^+$ , even when plasma or serum  $\text{K}^+$  is not appreciably reduced, intracellular and total body  $\text{K}^+$  stores can be depleted (Patrick, 1977; Brown, 1984). In rats subjected to dietary  $\text{Mg}^{2+}$  restriction, intramuscular  $\text{K}^+$  declined (Macintyre and Davidsson, 1958; Manitius and Epstein, 1963; Whang and Welt, 1963; Ginn et al., 1967; Dørup and Clausen, 1993). This was associated with decreased whole body  $\text{K}^+$  following prolonged (60-day) dietary  $\text{Mg}^{2+}$  restriction (Whang and Welt, 1963). In

human subjects given a low  $\text{Mg}^{2+}$  diet, urinary  $\text{K}^+$  excretion increased overall and total exchangeable  $\text{K}^+$  decreased (Shils, 1969). Intracellular  $\text{Mg}^{2+}$  depletion is thought to promote urinary  $\text{K}^+$  excretion through loss of voltage-dependent blockade of the outer medullary  $\text{K}^+$  channel (ROMK) in the kidney tubule, enhancing tubular  $\text{K}^+$  secretion (Huang and Kuo, 2007). Additionally, systemic  $\text{Mg}^{2+}$  depletion increases circulating aldosterone levels (discussed below), enhancing urinary  $\text{K}^+$  excretion in exchange for  $\text{Na}^+$  reabsorption.

Taken together, these findings suggest the hypothesis that  $\text{Mg}^{2+}$  depletion could contribute to urinary  $\text{Na}^+$  retention and increased blood pressure by stimulating NCC activity in the DCT. Surprisingly, rats given a low  $\text{Mg}^{2+}$  diet exhibit reduced NCC expression (Fanestil et al., 1999). Ferdaus et al. confirmed these findings in mice and found that dietary  $\text{Mg}^{2+}$  depletion reduced both total and phosphorylated NCC protein abundance in the kidney. NCC mRNA levels were unchanged, suggesting post-transcriptional effects on NCC expression. The hypothesis that dietary  $\text{Mg}^{2+}$  restriction may stimulate NCC degradation was supported by the observation that kidney-specific deletion of the ubiquitin ligase NEDD4-2 blocked downregulation of NCC by dietary  $\text{Mg}^{2+}$  restriction. Dietary  $\text{Mg}^{2+}$  depletion even blocked the ability of a  $\text{K}^+$ -restricted diet to increase total and phosphorylated-NCC protein abundance, providing further evidence that the influence of  $\text{Mg}^{2+}$  depletion on blood pressure is not NCC-mediated.

Systemic  $\text{K}^+$  depletion may influence  $\text{Na}^+$  handling in other portions of the nephron, such as the thick ascending loop of Henle. The  $\text{Na-K-Cl}$  co-transporter (NKCC2) in the thick ascending limb (TAL) is also modulated by intracellular WNK/SPAK/OSR1 pathway (Moriguchi et al., 2005; Rinehart et al., 2005; Liu et al., 2011; Richardson et al., 2011; Park et al., 2013; Terker et al., 2018; Marcoux et al., 2019). Given the ability of systemic  $\text{K}^+$  status to influence the WNK/SPAK/OSR1 pathway, it seems likely that differences in  $\text{Mg}^{2+}$  homeostasis may influence this pathway via changes in systemic  $\text{K}^+$ , but we are unaware of data directly exploring this hypothesis.

$\text{Mg}^{2+}$  could also influence  $\text{Na}^+$  reabsorption in the TAL through modulation of the calcium-sensing receptor (CaSR). Activation of the CaSR on the basolateral surface of cortical TAL cells reduces apical  $\text{K}^+$  channel activity (Wang et al., 1996). Impaired cellular  $\text{K}^+$  efflux impairs  $\text{Na}^+$  and  $\text{Cl}^-$  reabsorption through NKCC2, producing a loop diuretic-like effect.  $\text{Mg}^{2+}$ , like  $\text{Ca}^{2+}$ , can activate the CaSR, which may explain the earlier observation that intravenous  $\text{Mg}^{2+}$  infusion can decrease TAL  $\text{Na}^+$  reabsorption (Ploth et al., 1976). Whether changes in plasma  $\text{Mg}^{2+}$  within the physiologic range modulate CaSR activity and TAL  $\text{NaCl}$  reabsorption remains unclear.

## Renin-angiotensin-aldosterone system

Systemic  $\text{Mg}^{2+}$  status may also influence  $\text{Na}^+$  and  $\text{K}^+$  handling via modulation of the renin-angiotensin-aldosterone system. In laboratory animals, dietary  $\text{Mg}^{2+}$  restriction appears to stimulate aldosterone levels. Sapna et al. found that in rats, 6 days on low  $\text{Mg}^{2+}$  chow resulted in serum aldosterone of  $205.0 \pm 66.2$  pg/mL, which was not significantly higher than  $138.1 \pm 80.8$  pg/mL seen on control chow (Sapna et al., 2006). However, Laurant et al. observed an

increase in plasma aldosterone in rats given  $Mg^{2+}$ -deficient diet for two and 21 weeks (Laurant et al., 1999). Stimulation of aldosterone levels by dietary  $Mg^{2+}$  restriction seems to occur independently of extracellular fluid volume status, as dietary  $Mg^{2+}$  depletion continued to stimulate increased serum aldosterone even in animals given a high  $Na^+$  diet (Solounias and Schwartz, 1975).

Acute intravenous  $Mg^{2+}$  administration also reduces aldosterone levels. A study examining six “healthy,” normotensive volunteers infused  $MgSO_4$  at a rate of 0.6 mg/h (5 mEq/hr) and found that plasma aldosterone levels decreased to  $4 \pm 0.8$  ng/dL ( $111 \pm 22$  pmol/L) compared with  $6 \pm 0.2$  ng/dL ( $166 \pm 5.5$  pmol/L) in controls ( $p < 0.05$ ) (Ichihara et al., 1993). This occurred despite an increase in plasma renin activity. Corica et al. infused 3 gm (24 mEq) of  $MgSO_4$  into “healthy” volunteers and observed reduced serum aldosterone from  $18.97 \pm 11$  ng/dL ( $526 \pm 305$  pmol/L) to  $6.34 \pm 5$  ng/dL ( $176 \pm 139$  pmol/L) (Corica et al., 1996). This effect did not appear to be fluid volume mediated, as atrial natriuretic peptide levels did not change, and a control infusion with isotonic saline had no significant impact on aldosterone levels. Thus,  $Mg^{2+}$  sulfate infusion reduces aldosterone levels in humans, at least acutely.

Despite these observations, oral supplementation studies in humans have largely failed to demonstrate reduction in circulating aldosterone. One study gave 365 mg (15 mmol) of  $Mg^{2+}$ , as  $Mg^{2+}$  aspartate, to 17 subjects for 4 weeks (Cappuccio et al., 1985). Neither blood pressure nor aldosterone changed compared with participants receiving placebo. Participants had a mean baseline serum  $Mg^{2+}$  level of 2.16 mg/dL (0.89 mmol/L), as compared to a normal reference range for  $Mg^{2+}$  of 1.82–2.32 mg/dL (0.75–0.96 mmol/L) from the U.S. National Health and Nutrition Examination Survey I study (Lowenstein and Stanton, 1986). In another study of 15 untreated hypertensive individuals given 600 mg/day of  $Mg^{2+}$  in the form of  $Mg^{2+}$  oxide, blood pressure decreased, but no difference in aldosterone levels was observed (Sanjuliani et al., 1996). In a third study that provided 600 mg of  $Mg^{2+}$  daily as  $Mg^{2+}$  oxide to 17 subjects,  $Mg^{2+}$  decreased blood pressure but again failed to significantly reduce plasma aldosterone (Haga, 1992). In this study, baseline serum  $Mg^{2+}$  levels were 1.88–1.91 mg/dL (0.77–0.79 mmol/L). In these three studies, mean baseline aldosterone levels ranged from roughly 9–13 ng/dL (240–260 pmol/L). This is on the lower side of the reference range of 5–30 ng/dL (140–830 pmol/L) determined in healthy adults on an unrestricted  $Na^+$  diet (Al-Dujaili and Edwards, 1978). Thus, although  $Mg^{2+}$  supplementation did not reduce aldosterone levels, these findings may be influenced by the observation that study participants exhibited neither  $Mg^{2+}$ -depletion nor elevated aldosterone (e.g., from extracellular fluid volume depletion) at baseline.

Few studies have examined the response of aldosterone to oral  $Mg^{2+}$  supplementation in humans in the context of an aldosterone secreting stimulus, such as extracellular fluid volume depletion or a dietary  $K^+$  challenge. An exception is a study that measured aldosterone changes in response to an hour of exercise in nine men (Golf et al., 1984). Exercise increased plasma aldosterone from  $9.4 \pm 5.0$  ng/dL ( $260 \pm 140$  pmol/L) to  $19.1 \pm 13.7$  ng/dL ( $530 \pm 370$  pmol/L), perhaps secondary to either extracellular fluid volume depletion or increased plasma  $K^+$ . Two weeks of daily oral supplementation with 360 mg (15 mmol)  $Mg^{2+}$  as  $Mg^{2+}$  aspartate abrogated this increase in aldosterone, leading to aldosterone levels before and after exercise that were  $13.7 \pm 3.2$  ( $380 \pm 90$  pmol/L) and  $11.9 \pm 7.9$  ng/dL ( $330 \pm 220$  pmol/L), respectively. Whether oral

$Mg^{2+}$  supplementation influences aldosterone secretion in response to thiazide diuretics used for hypertension, which both deplete  $Mg^{2+}$  and stimulate aldosterone secretion through fluid volume contraction, seems likely, though unreported.

What are the mechanisms by which  $Mg^{2+}$  may modulate aldosterone secretion? This effect could be mediated by a direct influence upon aldosterone-secreting zona glomerulosa cells or via modulation of upstream components the renin-angiotensin-aldosterone system. A direct effect upon adrenal function is suggested by studies showing that  $Mg^{2+}$  exerted a voltage-dependent blockade of inwardly rectifying  $K^+$  and  $Ca^{2+}$  channels in adrenal glomerulosa cells (Vassilev et al., 1992; Lotshaw and Li, 1996). Activity of each of these channel types modulates aldosterone secretion. Furthermore, in cultured adrenal cells, higher extracellular  $Mg^{2+}$  reduced basal aldosterone secretion (Antonipillai et al., 1997). Extracellular  $Mg^{2+}$  also attenuates stimulation of aldosterone secretion by angiotensin II. In adrenal cells in culture, increased extracellular  $Mg^{2+}$  reduced angiotensin II-stimulated aldosterone release (Atarashi et al., 1989; Antonipillai et al., 1997). This effect was also observed *in vivo*, as rats given an infusion of angiotensin II in combination with  $Mg^{2+}$  sulfate exhibited diminished plasma aldosterone, as compared with rats given angiotensin II alone (Atarashi et al., 1990). Evidence for an influence of  $Mg^{2+}$  on angiotensin II-mediated aldosterone secretion in humans is provided by a study showing that 3 weeks on a very low (<1 mEq/day)  $Mg^{2+}$  diet augmented angiotensin II-stimulated aldosterone secretion (Rude et al., 1989). This increase in aldosterone secretion was partially rescued by acute intravenous  $Mg^{2+}$  repletion with  $Mg^{2+}$  sulfate. Together, these studies suggest that extracellular  $Mg^{2+}$  decreases sensitivity of adrenal glomerulosa cells to angiotensin II-stimulated aldosterone secretion.

Studies examining the influence of  $Mg^{2+}$  on upstream components of the renin-angiotensin-aldosterone system are more mixed. In laboratory rats, 14 weeks on a  $Mg^{2+}$ -deficient diet resulted in no difference in angiotensin II levels (Jin et al., 2013). However, another study examining rats on a  $Mg^{2+}$ -deficient diet for 6 days found increased angiotensin II, as well as increased plasma renin activity (Sapna et al., 2006). A third study examining dietary  $Mg^{2+}$ -restriction in rats found increased plasma renin activity at 2 weeks but not at 21 weeks (Laurant et al., 1999). In dogs given a low  $Mg^{2+}$  diet, plasma renin activity did not increase at any of several time-points through 90 days, although plasma aldosterone excretion did increase (Helber et al., 1972). In humans, serum  $Mg^{2+}$  was found to correlate directly with renin activity (Lind et al., 1989). In contrast, acute  $Mg^{2+}$  sulfate infusion increased plasma renin activity (Ichihara et al., 1993).

Taken together, these studies suggest that systemic  $Mg^{2+}$  depletion promotes aldosterone secretion without necessarily stimulating increased renin or angiotensin II levels. Whether this increase in aldosterone is reversible or leads to persistent aldosterone secretion (e.g., by promoting adrenal hyperplasia) remains unexplored. Although mechanisms discussed above suggest that systemic  $Mg^{2+}$  depletion should promote tubular reabsorption of  $Na^+$ , modulation of extracellular fluid volume by  $Mg^{2+}$  has not been described. In a study examining the impact of dietary  $Mg^{2+}$  depletion upon blood pressure and fluid volume in mice, although a  $Mg^{2+}$ -deficient diet increased blood pressure, it did not increase body fluid content, as measured using quantitative magnetic resonance (Pitzer Mutchler et al., 2023).

However, Na<sup>+</sup> overload promotes hypertension via mechanisms that may be Mg<sup>2+</sup>-sensitive, discussed below.

## Pro-hypertensive inflammatory processes

Na<sup>+</sup> can increase blood pressure via at least two pro-inflammatory mechanisms (Kirabo, 2017). First, high Na<sup>+</sup> diet increases oxidative stress in antigen-presenting cells (APCs). Peroxidation of arachidonic acid forms isolevuglandins (IsoLGs),  $\gamma$  ketoaldehydes capable of covalently modifying endogenous proteins. Modified proteins are presented at the APC surface, stimulating inflammation. Genetic prevention of IsoLG formation or pharmacologic scavenging of IsoLGs prevents salt-induced hypertension in mouse models (Kirabo et al., 2014; Barbaro et al., 2017). Second, high Na<sup>+</sup> diet increases expression of NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3), a key component of the inflammasome, in the renal medulla and other tissues (Zhu et al., 2016). The NLRP3 inflammasome catalyzes the production and secretion of the proinflammatory cytokines, IL-1 $\beta$  and IL-18 (Elijovich et al., 2021). Genetic or pharmacologic impairment of the NLRP3 inflammasome prevented blood pressure increases in mouse models of hypertension (Wang et al., 2014; Pitzer et al., 2022).

A Mg<sup>2+</sup>-deficient diet activates these hypertension-promoting inflammatory processes. In laboratory animals, dietary Mg<sup>2+</sup> deficiency stimulates leukocytosis and circulating inflammatory cytokine levels (Weglicki et al., 1992; Malpuech-Brugère et al., 2000; Van Orden et al., 2006). Oral Mg<sup>2+</sup> supplementation in humans suppresses circulating C-reactive protein (Mazidi et al., 2018). In mice experiencing hypertension in response to dietary Mg<sup>2+</sup> restriction, circulating IL-1 $\beta$  levels increase (Pitzer Mutchler et al., 2023). NLRP3 and IsoLG positivity in splenic and renal dendritic cells increase to levels comparable to a high Na<sup>+</sup> diet. Whether hypertension induced by dietary Mg<sup>2+</sup> depletion is dependent upon activation of the NLRP3 inflammasome or production of IsoLGs was not examined, but these findings are consistent with a contribution of Mg<sup>2+</sup> depletion to hypertension-promoting inflammation. Interesting questions remain regarding the mechanisms by which dietary Mg<sup>2+</sup> restriction induces inflammation and whether dietary Mg<sup>2+</sup> supplementation protects against high salt diet-mediated inflammation and hypertension.

## Clinical implications

The likely contributions of Mg<sup>2+</sup>-deficiency to increased blood pressure and to other aspects of cardiovascular disease suggest that optimal management of hypertension should include attention to Mg<sup>2+</sup> balance. Clinicians should have a high index of suspicion for Mg<sup>2+</sup>-depletion in hypertensive patients, given that 1) dietary Mg<sup>2+</sup> deficiency is common (USDA Agricultural Research Service, 2019), 2) hypertension is associated with Mg<sup>2+</sup> depletion, even in untreated patients (Rodríguez-Moran and Guerrero-Romero, 2014; Rodríguez-Ramírez et al., 2015), 3) common comorbidities (such as diabetes mellitus) are also associated with Mg<sup>2+</sup> depletion (Ray et al., 2023), and 4) commonly prescribed medications promote Mg<sup>2+</sup> deficiency, including thiazide-type and loop diuretics, and proton pump inhibitors (Ray et al., 2023). Clinicians should not rely solely upon

measurement of plasma Mg<sup>2+</sup> levels for determination of Mg<sup>2+</sup> depletion, since 1) less than 1% of bodily Mg<sup>2+</sup> resides in the plasma, so that plasma Mg<sup>2+</sup> levels do not faithfully reflect bodily Mg<sup>2+</sup> stores, and 2) “normal” reference ranges typically used for plasma Mg<sup>2+</sup> are likely inappropriately low (Costello et al., 2016; Micke et al., 2021). Clinicians should consider prescription of a well-absorbed oral Mg<sup>2+</sup> supplement. Well-absorbed supplements include most organic salts and possibly the chloride salt, as discussed elsewhere (Ray et al., 2023). Clinicians should have a low threshold for prescribing agents that oppose urinary Mg<sup>2+</sup>-wasting, such as K<sup>+</sup> and Mg<sup>2+</sup>-sparing diuretics (e.g., spironolactone or amiloride), and SGLT2 inhibitors (Ray et al., 2020). It is likely that improved Mg<sup>2+</sup> balance associated with these agents contributes to improved cardiovascular benefits associated with their use (Ray, 2020).

## Conclusion

Mg<sup>2+</sup> depletion likely promotes increased blood pressure via numerous mechanisms, described above, including effects on the sympathetic nervous system, vascular tone, the RAAS system, systemic Na<sup>+</sup> and K<sup>+</sup> balance, and inflammatory processes. Given the widespread prevalence of Mg<sup>2+</sup> depletion and the tendency of some approaches to treating hypertension to induce Mg<sup>2+</sup>-depletion, attention to systemic Mg<sup>2+</sup> deficiency has the potential to improve clinical management of hypertension and cardiovascular outcomes.

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ZA: Writing—original draft, writing—review and editing. ER: Conceptualization, funding acquisition, writing—original draft, writing—review and editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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