Diabetology &
Metabolic Syndrome

REVIEW

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Hypomagnesemia: exploring its multifaceted health impacts and associations with blood pressure regulation and metabolic syndrome

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Abstract

This article provides a comprehensive and in-depth exploration of the multifaceted effects of Hypomagnesemia on human health, with a specific focus on its intricate associations with mechanisms regulating blood pressure and metabolic syndrome. Firstly, the fundamental concept of hypomagnesemia is elucidated, followed by a detailed analysis of its prevalence, risk factors, and Magnesium Deficiency Score. Furthermore, this article delves into the intricate relationship between hypomagnesemia and blood pressure regulation, encompassing its impact on endothelial function, vascular calcification, oxidative stress and inflammatory response, sympathetic nervous system activity as well as the renin–angiotensin–aldosterone system (RAAS). Additionally, it explores the correlation between hypomagnesemia and insulin resistance, metabolic syndrome along with other health issues. Notably noteworthy is that this paper also places special emphasis on exploring the potential role of hypomagnesemia in specific diseases such as renal hypertension and preeclampsia while providing novel insights for their prevention and treatment. Finally, this article summarizes the diverse effects of hypomagnesemia on health while anticipating future research directions. Future studies should further investigate the pathogenesis underlying hypomagnesemia while optimizing assessment methods for magnesium deficiency to develop targeted intervention strategies aimed at offering improved treatment options alongside preventive measures for patients.

Keywords Hypomagnesemia, Hypertension, Health, Metabolic syndrome

Introduction

Magnesium, the fourth most abundant mineral element in the human body, serves as an essential cofactor for over 300 enzymes and more than 800 proteins. It plays a pivotal role in fundamental life activities such as ATP generation, oxidative phosphorylation, glycolysis, and mitochondrial function. Recent studies have further untangled that magnesium, through its anti-inflammatory and antioxidant properties, can effectively induce vasodilation and possesses neuroprotective and immunomodulatory functions. Additionally, it is crucial for maintaining bone density,

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regulating glucose metabolism, improving neuropsychiatric symptoms, and regulating blood pressure [1, 2].

Hypertension (HTN), a leading cause of global morbidity and mortality [3], remains poorly controlled, with only one-fifth of patients achieving adequate blood pressure management, and even lower rates in low- and middle-income countries. The number of adult patients with HTN has been increasing from 1990 to 2019 [4]. The traditional HTN threshold is 140/90 mmHg, but new guidelines define normal blood pressure as below 120/80 mmHg [5]. However, such a definition increases the HTN rate among American adults from 32 to 46% [6].It's worth noting that even within the normal blood pressure range [7], there can be adverse health effects. Studies have shown that blood pressure higher than 110/70 mmHg is associated with increased mortality from coronary heart disease and stroke [8]. For individuals with normal blood pressure, every sustained 2 mmHg reduction in blood pressure may significantly reduce the risk of disabling stroke and early death from vascular causes [9]. The prevalence of HTN is still rising, while awareness, treatment, and control rates remain problematic [10].

In recent years, numerous studies have indicated a significant correlation between magnesium deficiency and the risk of HTN [11]. The mechanisms involved include vascular tone regulation, improvement in insulin sensitivity, and inhibition of the sympathetic nervous system [12]. Clinical investigations have untangled a notable dose–response relationship between serum magnesium levels and HTN risk: for every 0.5 mg/dL increase in serum magnesium, the risk of HTN decreases by 7%. It is worth noting that this protective effect is most pronounced within the serum magnesium concentration range of 1.6–3.5 mg/dL, exhibiting a U-shaped curve beyond this range. However, there is considerable heterogeneity among existing studies ($I^2 = 81.1\%$), potentially attributed to factors such as population differences and variations in measurement methods [13]. A recent meta-analysis has further confirmed that magnesium supplementation can significantly reduce systolic and diastolic blood pressure by 5.6 mmHg and 2.8 mmHg, respectively. This hypotensive effect is more pronounced in patients with baseline magnesium deficiency (serum magnesium < 1.8 mg/dL) or resistant hypertension ($p < 0.05$) [14].This article aims to systematically review the pathological association between magnesium deficiency and HTN and explore the potential value of precise magnesium supplementation strategies based on the latest clinical evidence.

Hypomagnesemia

The overlooked hypomagnesemia

Mild magnesium deficiency is often overlooked, but when the condition intensifies, it can trigger neuromuscular, cardiac, and nervous system dysfunction. Because the symptoms of hypomagnesemia overlap with those of various other diseases, magnesium deficiency is frequently misidentified as a secondary consequence rather than a primary health issue [15]. HTN and magnesium deficiency often coexist as comorbidities [16]. Accurately assessing the prevalence of hypomagnesemia, designing and implementing potential interventions using artificial intelligence and machine learning techniques, and developing novel predictive analytics tools and laboratory medicine methods are crucial for improving the management of chronic diseases such as hypertension.

Magnesium intake is generally below the recommended health standards. Metabolic balance data suggest that the actual requirement for a 100 kg adult should reach 335 mg/day, yet 74% of overweight/obese patients and 45.2% of adults have insufficient intake. Coupled with dietary patterns that are difficult to meet these needs, magnesium deficiency has become a significant public health concern [17]. It is estimated that approximately 10% to 30% of the population suffers from subclinical magnesium deficiency. Even individuals with seemingly normal serum magnesium concentrations may still be magnesium deficient, and this condition is more severe among those with hypertension [12]. The traditional cut-off of 0.75 mmol/L may not adequately reflect true magnesium nutritional status. Studies have shown that when plasma magnesium concentrations are maintained at or above 0.85 mmol/L, the risk ratios for elevated metabolic syndrome and blood pressure (BP) indicators are significantly lower than 1, indicating a negative correlation between higher plasma magnesium concentrations and these metabolic abnormalities [18]. Further research has found that for patients already diagnosed with metabolic syndrome but with normal blood magnesium levels, oral magnesium supplementation can also lead to a decrease in physiological indicators such as blood pressure, further confirming the important role of magnesium in regulating human metabolism and cardiovascular health.

Therefore, it has been suggested to raise the lower limit of the reference range for serum magnesium from 0.75 mmol/L to 0.85 mmol/L to more accurately reflect the body's magnesium requirements and potential magnesium deficiency states [18, 19]. This adjustment not only helps to increase clinicians' and the public's awareness of magnesium nutritional status but also provides a scientific basis for developing more effective magnesium supplementation strategies, thereby further reducing the risk of chronic diseases such as cardiovascular disease.

However, the implementation of this recommendation requires more clinical research and data support to ensure its accuracy and feasibility.

Risk factors

Serum magnesium exists in three main forms in the human body: protein-bound, ionized, and anionic [20]. Magnesium is primarily absorbed through the paracellular pathway (accounting for 90%) in the small intestine (duodenum and ileum) and the transcellular pathway (accounting for 5%, possibly higher during low Mg^{2+} conditions) in the colon. Paracellular absorption depends on luminal Mg^{2+} concentration and is regulated by tight junction proteins (such as claudin-2/7/12), while transcellular absorption is mediated by transient receptor potential channel M subfamily members 6/7 (TRPM6/7) channels (activated by epidermal growth factor and insulin) and involves basolateral extrusion via cyclin M4 (CNNM4) (affected by FGF23 and PTH) [21]. Gut microbiota acidifies the colonic environment through fermentation, enhancing magnesium solubility and promoting its absorption through TRPM6 channels [22]. However, butyrate inhibits TRPM6 channels, reducing magnesium uptake, so low concentrations of butyrate may be beneficial for magnesium-deficient patients [23]. Notably, many bacteria contain sensor proteins that detect extracellular magnesium concentrations [24], and a high-magnesium environment can promote the growth and metabolism of Akkermansia muciniphila. This interaction further emphasizes the role of magnesium in connecting and integrating the gut microbiota ecosystem [25].

As global dietary habits gradually shift towards westernization, dietary intake of magnesium has shown a declining trend. Processed foods, filtered or deionized drinking water, and foods grown in magnesium-deficient soils all contribute to inadequate magnesium intake [26]. The causes of magnesium deficiency are not limited to reduced dietary intake but also include various preexisting pathological states, such as impaired gastrointestinal absorption, kidney disease, electrolyte imbalances, alcohol abuse, and medication use, all of which can lead to chronic magnesium deficiency [27–30]. Additionally, aging significantly affects magnesium deficiency. Although the magnesium requirements remain relatively stable across age groups, magnesium intake is generally insufficient among older adults. With increasing age, both magnesium absorption efficiency and the kidney's ability to reabsorb magnesium decline [31]. In older adults, magnesium imbalance may increase their risk of developing age-related diseases [32, 33]. There is a positive correlation between dietary magnesium intake and telomere length in hypertensive patients, and this association is particularly significant among those aged 45 above, revealing a potential mechanistic link between biological aging processes and HTN [34]. agnesium deficiency remains a frequently overlooked and widespread health issue in modern society. Both subclinical and chronic magnesium deficiencies can lead to various dysfunctions and diseases, and low magnesium levels are often observed in hypertension, arrhythmia, coronary artery disease, metabolic syndrome, and other conditions. Maintaining appropriate magnesium levels plays a crucial role in human health [35].

Primary magnesium deficiency	Secondary magnesium deficiency
Inadequate dietary intake	Digestive system diseases
Impaired magnesium absorption	Kidney diseases and drugs that cause renal tubular damage
Excessive renal loss	Endocrine and metabolic diseases
Impaired magnesium utilization	Other factors such as age and gender

Magnesium deficiency score

The Magnesium Deficiency Score (MDS) represents a novel tool for assessing magnesium status, designed based on four major clinical risk factors that impact renal magnesium reabsorption: alcohol consumption, diuretic use, proton pump inhibitor (PPI) use, and renal function impairment [36]. These factors contribute to disruptions in magnesium homeostasis through various mechanisms, with notable synergistic effects observed between alcohol intake and combined diuretic/PPI use, further promoting magnesium-calcium loss. The MDS grading system (low: 0–1; medium: 2; high: 3–5) facilitates a refined evaluation of patients' magnesium depletion status, enabling the tailoring of individualized treatment plans. Numerous studies have demonstrated a significant association between higher MDS levels and increased incidence of various diseases, including cardiovascular and renal disorders [36, 37].

In recent years, correlations between MDS and high-risk factors for hypertension, such as sleep apnea [38],metabolic dysfunction [39, 40],renal damage [41], depression [42] and diabetes [43], have also been reported. With each unit increase in MDS level, the risk of developing HTN also escalates, further emphasizing the MDS's crucial role in predicting HTN risk [44]. Multiple studies have shown a significant link between MDS and the prognosis of HTN patients. In a study involving 12,485 individuals [45], patients with HTN and cardiovascular disease (CVD) exhibited significantly higher all-cause and cardiovascular mortality rates as MDS levels increased. These patients often present with more severe clinical conditions, including multiple comorbidities and functional impairments, leading to poorer outcomes and

potentially amplifying the effects of magnesium deficiency [44, 46]. Frequent use of medications like diuretics in CVD patients may further exacerbate magnesium depletion issues. The MDS not only closely correlates with mortality in HTN patients but also serves as a good predictor of prognosis in different populations. In patients with chronic kidney disease (CKD), MDS levels are independently associated with higher long-term cardiovascular and all-cause mortality rates [47]. These findings suggest that MDS and magnesium intake can further predict and improve the prognosis and all-cause mortality of chronic diseases, allowing for reasonable magnesium intake assessment [36].

The MDS offers significant advantages over traditional serum magnesium testing. Firstly, it integrates multiple clinical risk factors to provide a more comprehensive magnesium status evaluation [40]. Secondly, as a cost-effective initial screening tool, its simple composition of indicators is particularly suitable for large-scale screening in resource-limited areas. Furthermore, it is applicable for dynamic monitoring of high-risk populations. Research has confirmed that combining the MDS with demographic characteristics (such as gender and age) in predictive models can effectively identify high-risk groups for magnesium deficiency associated with systemic inflammation and increased CVD mortality.

This model has demonstrated two major clinical application values: improving the accuracy of chronic disease risk prediction through combined dietary magnesium intake assessment and providing a basis for precision nutritional interventions, such as magnesium supplementation strategies targeting individuals with abnormal MDS. Future research can explore the optimal role of combining MDS with biomarkers (serum magnesium/urinary magnesium) in evaluating magnesium status [36].However, the MDS also has limitations: it cannot directly reflect intracellular magnesium concentration and is influenced by dietary components [37], and it does not cover all medications that may affect magnesium metabolism [19, 48]. Notably, more prospective studies are needed to elucidate the interactions between MDS and factors like gender and age.

The relationship between hypomagnesemia and blood pressure regulation

Association between low magnesium and endothelial function

Endothelial-derived vasodilation mechanisms play a crucial regulatory role primarily in small resistance vessels. Endothelial cells control the dilation function of vascular smooth muscle cells (VSMCs) by releasing vasodilatory signaling molecules, including nitric oxide (NO), prostaglandins, and endothelial-derived hyperpolarizing factor (EDHF), thereby maintaining vascular tone. Studies have shown that magnesium ions (Mg^{2+}) can enhance endothelium-dependent dilation through various pathways, including stimulating the expression and activity of endothelial nitric oxide synthase (eNOS) [49] and promoting the phosphorylation of protein kinase B (Akt) [50], thus activating the NO signaling pathway. This Mg^{2+}-induced NO release may be one of the essential mechanisms for local vasodilation. However, in hypertensive states, EDHF/NO-mediated vasodilation is often impaired [51], leading to increased vasoconstriction and elevated peripheral resistance.

At the cellular structural level, tight junctions (TJs) are vital for maintaining the barrier function of endothelial and epithelial tissues [52]. The integrity of the TJ complex, with zona occludens (ZO) serving as a scaffolding molecule, determines the selective permeability and signal transduction functions of TJs. When the TJ complex is damaged, it can lead to abnormal macromolecular transport and loss of cell polarity, potentially inducing various pathological changes. Recent studies have revealed that intracellular proteins can form functional microdomains through phase separation mechanisms, promoting molecular condensation and efficient biochemical reactions. Among these, abnormal phase separation of ZO-1 protein may contribute to paracellular permeability defects and ion transport disorders, which could be one of the critical mechanisms linking hypertension and hypomagnesemia [53].

Endothelial dysfunction (ED) is a key factor in the pathogenesis of hypertension and is significantly positively correlated with the risk of cardiovascular events [54]. As ED severity increases, cardiovascular risk further escalates. Additionally, ED can promote structural remodeling of small resistance vessels, indicating that endothelial dysfunction and vascular remodeling in resistance arteries are closely related to the development and progression of cardiovascular diseases [55, 56]. Magnesium supplementation has shown positive effects in this area, mitigating the adverse impacts of hypertension by enhancing endothelial function [57]. Conversely, magnesium deficiency can exacerbate ED, making endothelial cells more susceptible to oxidative stress damage and further worsening vascular function[58].

The association between low magnesium and vascular smooth muscle

Based on the arterial mechanical model of the pressure-diameter relationship, it has been found that when vascular smooth muscle (VSM) is stiffer than the extracellular matrix (ECM), an increase in VSM tension leads to increased arterial hardness [59]. This hardness increase reduces arterial elasticity, elevating systolic

blood pressure and consequently increasing the workload on the heart. The development and progression of hypertension are closely related to the contractile state of vascular smooth muscle cells (VSMCs) [10], and magnesium ions regulate VSMC function through multiple pathways, playing a key role in maintaining vascular tone balance [60, 61].

Magnesium may directly affect VSMCs or influence K^+ channels (IKCa and SKCa) through EDHF, inducing cell membrane hyperpolarization and thereby mediating vasodilation [62]. The molecular mechanism involves processes such as G-protein coupled receptor activation, promotion of calcium efflux, and inhibition of calcium influx [63]. Studies have shown that the vasodilatory effect of magnesium is concentration-dependent, with 2.4 mmol/L causing 16% more vasorelaxation than 0.9 mmol/L, and the effect is more significant on α1-receptor-mediated contraction [64, 65]. In pathological states such as pulmonary hypertension (PH), disturbances in ion channel homeostasis can exacerbate vascular dysfunction [66]. The specific functions of different magnesium transporters may be reflected in differences in their physiological regulatory processes [67, 68]. As one of the magnesium transporters in the vascular system, TRPM7 expression is reduced in hypertension [69], potentially impacting vascular structure [70].

The Na+/K+-ATPase consists of four tissue-specific α-subunits (α1-α4) [71]. The α2 subtype is located on the vascular smooth muscle plasma membrane close to the Na^+,Ca^{2+} exchanger (NCX) [72, 73]. Approximately 50% of patients with primary hypertension have elevated levels of endogenous ouabain, a cardiotonic steroid [74]. Endogenous ouabain can inhibit Na^+,K^+-ATPase by binding to the α-subunit and phosphorylating the E2 state. This may affect local Na+ concentrations, activating cSrc kinase and phosphorylating the myosin phosphatase target subunit 1 (MYPT 1) of vascular smooth muscle, leading to "Ca^{2+} sensitization" phenomena that enhance VSMC contraction, increase peripheral resistance, and elevate blood pressure [75]. Magnesium regulates vascular tone by altering Na^+,K^+-ATPase activity, which is crucial for maintaining the relaxed state of VSMCs [57]. When extracellular or systemic magnesium levels decrease, it can cause vasospasm, reducing microvascular blood flow.

In the process of vascular calcification (VC), magnesium exerts a protective effect by inhibiting the formation of hydroxyapatite and regulating calcium-phosphorus metabolism balance [76, 77]. VC can be divided into intimal calcification and medial calcification, with the latter closely related to arteriosclerosis and systolic HTN [78]. Magnesium deficiency promotes the transformation of VSMCs into an osteoblast-like phenotype, accelerating the calcification process [79, 80].

The activation of the WNT/β-catenin pathway is associated with the development of hypertension and vascular calcification [81, 82]. Inhibition of this signaling pathway can slow or prevent the progression of vascular calcification. Magnesium supplementation has been shown to inhibit the WNT/β-catenin signaling pathway through a TRPM7-dependent pathway, reducing gene expression associated with matrix calcification [83]. However, in chronic kidney disease, reducing TRPM7 can prevent calcification [84].

In summary, magnesium regulates VSMC function through multiple targets, playing a key role in maintaining vascular tone balance and inhibiting pathological remodeling. Its concentration-dependent effects and pathway-specific actions provide potential targets for the prevention and treatment of hypertension and vascular calcification.

The association of low magnesium with oxidative stress and inflammation

The association between magnesium deficiency and oxidative stress

When magnesium is deficient, there is an increase in free radical production in different tissues, accompanied by a decrease in both the expression and activity of antioxidant enzymes. This leads to an elevation of superoxide anions and hydrogen peroxide produced by inflammatory cells, further exacerbating oxidative tissue damage. Magnesium deficiency also interferes with the release of NO from coronary artery endothelium and the activation of neuronal nitric oxide synthase, reducing serum magnesium and tissue glutathione levels in all heart chambers. This deficiency also results in decreased ATP and induces an increase in NADPH oxidase activity. In response to low serum magnesium levels, magnesium transporters may be triggered, inducing intracellular magnesium efflux to increase serum magnesium concentrations. However, this process may further reduce intracellular magnesium content, altering cell signaling functions. The reduction of intracellular magnesium may also trigger the release of magnesium from mitochondrial stores through specific pathways (such as SLC41A3), exacerbating abnormalities in mitochondrial signaling and function related to magnesium and ATP [22].

Mitochondria serve as the central hub for energy metabolism and reactive oxygen species (ROS) generation in cardiomyocytes, while also functioning as a significant intracellular storage reservoir for magnesium ions. Research indicates that, in cardiac tissue under magnesium deficiency, mitochondrial oxidative stress levels increase significantly despite no notable changes

in the expression levels of antioxidant proteins. This suggests that the mitochondrial electron transport chain may be the primary source of excessive ROS production [85]. In diabetic mouse models, magnesium deficiency markedly exacerbates mitochondrial oxidative stress and induces diastolic dysfunction. However, treatment with mitoTEMPO (a mitochondria-targeted antioxidant) and magnesium supplementation effectively ameliorates oxidative stress and reverses abnormalities in diastolic function [86]. Magnesium ions play multiple protective roles in the mitochondrial antioxidant defense system: firstly, they efficiently suppress the excessive generation of mitochondrial ROS, maintaining the stability of the mitochondrial membrane potential; secondly, by regulating the opening of the mitochondrial permeability transition pore (mPTP), they reduce the release of cytochrome C; furthermore, magnesium also modulates mitochondrial calcium homeostasis, preventing calcium overload. At the molecular level, magnesium ions can upregulate the expression of anti-apoptotic proteins belonging to the BCL-2 family while downregulating the expression of pro-apoptotic proteins. They alleviate cell apoptosis by inhibiting the activation of HIF-1α and the P38/JNK signaling pathway, and moderately regulate the autophagy process. It's worth noting that magnesium also effectively blocks the activation of NF-κB, reducing the production of pro-inflammatory cytokines and chemokines [87]. Future research should investigate the impact of TRPM7 kinase on mitochondrial function and its association with mitochondrial dysfunction and inflammation. This may provide insights into the mechanisms underlying mitochondrial dysfunction caused by low magnesium.

The association between magnesium deficiency and inflammation

Inflammation is a physiological response to cell damage, and biomarkers of inflammation are elevated in patients with HTN, contributing to the pathogenesis of the disease [88]. Inflammation not only leads to increased blood pressure but also causes end-organ damage associated with this condition. Inflammation can be both a cause and a consequence of HTN [89]. Inflammation increases the production of peroxynitrite, which damages cellular biomolecules and structures. Additionally, inflammation can affect host metabolic processes such as lipid oxidation. Inflammation also plays a key role in regulating blood pressure, particularly in the hypertensive effects of a salt-rich diet [90]. NLRP3 inflammasome, through caspase-mediated cleavage or IL-1β-mediated mechanisms, inhibits IL-33 signaling and is involved in this process. Reducing NLRP3 activity can alleviate HTN [91]. Magnesium deficiency leads to the activation of phagocytic cells, triggering a series of inflammatory responses. These include disturbances in calcium channel blocking, increased intracellular calcium concentrations, activation of N-methyl-D-aspartate (NMDA) receptors, and activation of cellular inflammatory responses. These changes result in the release of various pro-inflammatory factors and stimulate the production of acute-phase proteins [92, 93]. The risk of hypertension increases with elevated plasma levels of IL-6 and C-reactive protein [94].

In the pathological state of obesity, the body exhibits chronic low-grade inflammation characterized by abnormally elevated levels of free fatty acids (FFAs) due to lipid accumulation. FFAs exacerbate oxidative stress through a dual mechanism: activating the NADPH oxidase system and inhibiting endogenous antioxidant gene expression, both leading to increased production of ROS. It is noteworthy that FFAs can activate Toll-like receptor signaling pathways through interaction with macrophages, promoting the nuclear translocation of key inflammatory transcription factors such as NF-κB and triggering a systemic inflammatory cascade. This process involves the overexpression of adhesion molecules like vascular cell adhesion molecule-1 (VCAM-1), and various chemokines, which facilitate the adhesion, rolling, and migration of leukocytes within the vascular endothelium, ultimately resulting in inflammatory infiltration of the vessel wall and tissue remodeling [58]. Magnesium ions play multiple protective roles in regulating this inflammatory network. Firstly, they downregulate the expression of proinflammatory cytokines by inhibiting the activation of the NF-κB signaling pathway. Secondly, magnesium maintains mitochondrial function stability, reducing ROS production. Furthermore, it regulates calcium ion channels to block inflammatory signal transmission [58].

Magnesium deficiency may directly trigger chronic inflammation or indirectly induce it by altering the gut microbiota [95]. An in-depth animal study found that a low-magnesium diet significantly reduced the number of bifidobacteria and decreased the mRNA expression of intestinal barrier components, accompanied by elevated levels of inflammatory cytokines. During colitis, compared to reducing dietary magnesium content, magnesium supplementation effectively buffered changes in gut microbial richness and shaped a different microbial community structure from that observed during colitis [96]. Magnesium compounds can restore altered bacterial composition and abundance, regulate the expression of inflammatory molecules and chemokines, and improve inflammatory responses and leukocyte migration [97–99].

Magnesium deficiency contributes to the pathogenesis of various metabolic diseases by promoting oxidative stress and inflammatory responses. Magnesium supplementation may exert protective effects through

antioxidation, anti-inflammation, and regulation of the gut microbiota, although further clinical research is needed to validate its specific applications [100].

Association between hypomagnesemia and the sympathetic nervous system

The guidelines published by the European Society of Cardiology/European Society of HTN in 2018 further emphasized the association between cardiovascular risk in hypertensive patients and adrenergic activation [101]. Magnesium deficiency promotes excessive activation of the sympathetic nervous system through multiple mechanisms: Firstly, by antagonizing Ca^{2+}, it weakens the inhibitory effect on catecholamine release from the adrenal medulla and sympathetic nerve endings, leading to increased secretion of norepinephrine and epinephrine. Simultaneously, magnesium deficiency reduces adenosine cyclase activity, decreasing cyclic adenosine monophosphate (cAMP) production and further elevating catecholamine levels [102]. Secondly, magnesium deficiency, as an endogenous blocker of N-methyl-D-aspartate (NMDA) receptors, leads to receptor disinhibition, and increased Ca^{2+} influx enhances central sympathetic output, manifesting as increased heart rate and vasoconstriction [1, 103]. Thirdly, decreased magnesium-dependent COMT enzyme activity reduces catecholamine degradation, promoting salt sensitivity and hypertension [104]. It's worth noting that the enzyme activation process of COMT is absolutely dependent on the presence of Mg^{2+}, so Mg^{2+} deficiency can easily trigger salt-sensitive hypertension [105]; it also reduces the vasoprotective mediator 2-methoxyestradiol (2-ME) and upregulates the AT1R/SPAK/NCC signaling pathway [106, 107]. Finally, hypomagnesemia promotes the release of proinflammatory factors, activating the sympathetic nerves. Sympathetic excitation, in turn, exacerbates the inflammatory response through β-receptors. Simultaneously, reduced antioxidant enzyme activity leads to the accumulation of free radicals, damaging the autonomic nerve center, forming a vicious cycle of inflammation-oxidative stress-sympathetic activation [108].

The pathophysiology of hypertension caused by SNS overactivation due to magnesium deficiency can be explained from both acute and chronic perspectives. In the acute phase, there is a significant increase in SNS excitability, prompting massive catecholamine release, leading to vasoconstriction and tachycardia, thereby increasing cardiac output and peripheral vascular resistance, resulting in acute elevation of blood pressure. The chronic phase involves multiple pathophysiological changes: on the one hand, it enhances salt sensitivity and promotes renal sodium reabsorption, causing blood volume expansion; on the other hand, inflammation and oxidative stress-mediated vascular endothelial dysfunction lead to vascular remodeling, continuously increasing peripheral resistance; simultaneously, long-term upregulation of central sympathetic nerve tension further disrupts blood pressure regulation homeostasis. These mechanisms collectively constitute a vicious cycle of "enhanced catecholamine effect—central sympathetic drive hyperactivity—renal sodium retention—inflammatory oxidative stress," ultimately leading to the continuous progression of hypertension. Based on this, magnesium supplementation therapy may become a potential intervention strategy for the prevention and treatment of HTN, especially salt-sensitive and sympathetically hyperactive HTN, by correcting the aforementioned pathological links.

Association between hypomagnesemia and the renin–angiotensin–aldosterone system (RAAS)

Excessive aldosterone stimulates endothelial dysfunction and inflammatory cell infiltration, promoting the development of atherosclerotic plaques, as well as arteriosclerosis and calcification [109]. Relevant studies have shown a close association between abnormal aldosterone regulation and hypomagnesemia [110]. Specifically, low levels of magnesium can prompt aldosterone upregulation and further lead to hypertension by downregulating the function of the TRPM7 transporter. This series of reactions can also exacerbate magnesium deficiency [111]. Conversely, magnesium supplementation can effectively reduce serum aldosterone levels. When aldosterone escape occurs, segmental sodium transport is inhibited, which may be related to reduced magnesium reabsorption [112]. In addition, magnesium supplementation seems to affect aldosterone secretion produced by thiazide diuretics used to treat hypertension. These diuretics not only lead to magnesium depletion but also stimulate aldosterone secretion through a fluid contraction mechanism. Magnesium may exert this effect by directly influencing glomerular cells that secrete aldosterone or by regulating the upstream renin–angiotensin–aldosterone system [113]. Magnesium also helps activate vitamin D as a cofactor for enzymes involved in vitamin D metabolism. Adequate magnesium levels ensure the function of these enzymes, thereby improving the utilization of active vitamin D. Long-term vitamin D deficiency can lead to hyperactivation of the RAAS, which is one of the important mechanisms of blood pressure regulation [114].

Interestingly, while magnesium depletion can promote aldosterone secretion, it does not necessarily lead to increased levels of renin and angiotensin II

[32]. Whether this increase in aldosterone is reversible or leads to continuous secretion remains to be further explored. Additionally, how the reduction of extracellular Mg^{2+} precisely activates relevant cellular mechanisms is an important direction for future research (Fig 1).

Hypomagnesemia and insulin resistance

Magnesium influences insulin sensitivity and β-cell function through multiple mechanisms. At the molecular level, magnesium ions directly promote insulin secretion by modulating key elements such as glucokinase, ATP-sensitive potassium (KATP) channels, and L-type calcium channels. Simultaneously, they enhance insulin

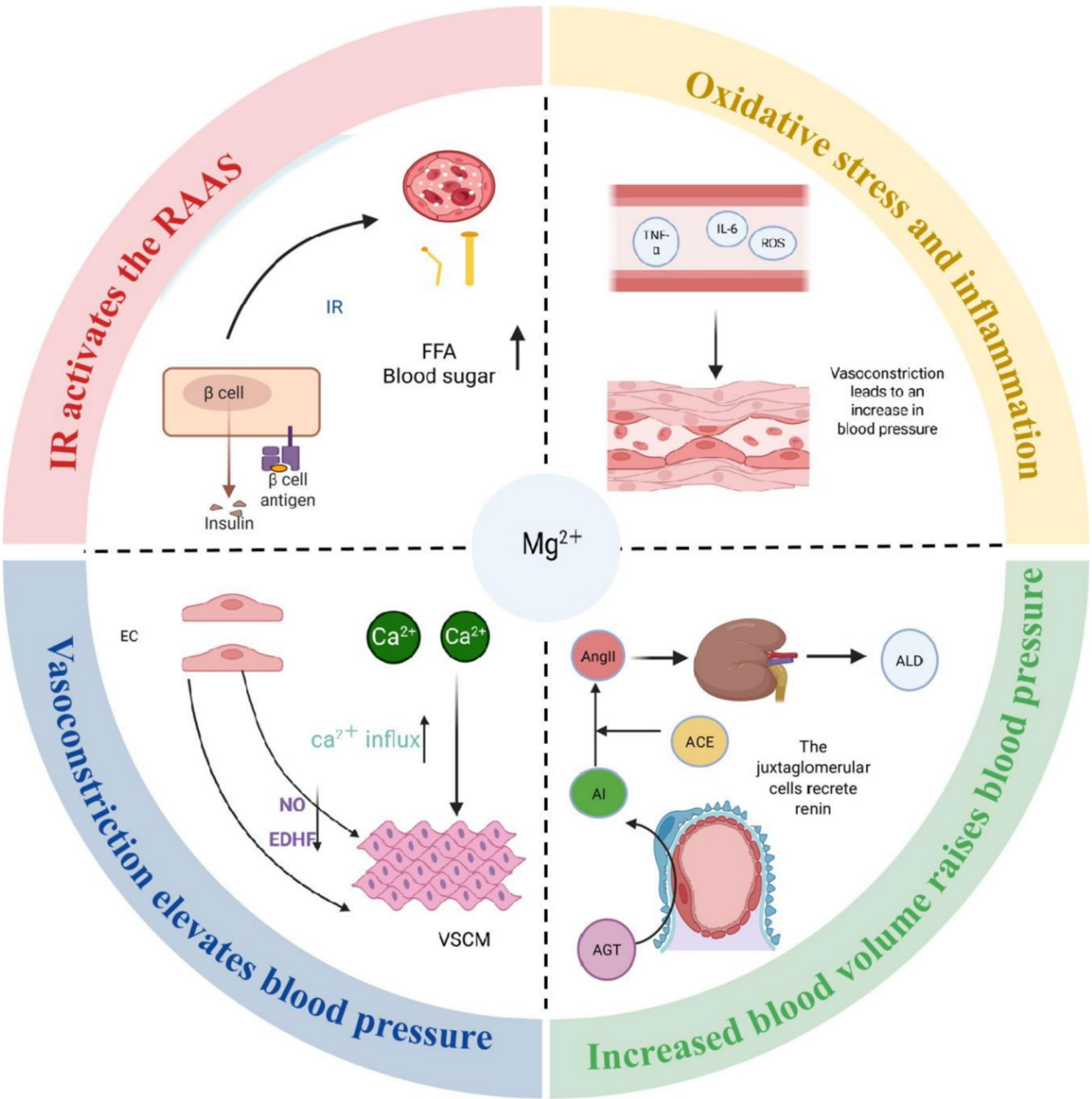

Fig. 1 Magnesium deficiency weakens calcium antagonism, enhances NADPH oxidase activity, leading to increased oxidative stress [22], inhibits eNOS activity, and reduces NO production, causing endothelial dysfunction [49]. Simultaneously, it diminishes the inhibition of calcium channels, increases calcium influx, and vasoconstriction of vascular smooth muscle, and exacerbates vascular tension by reducing Na^{+}-K^{+}-ATPase activity [57]. Furthermore, low magnesium activates the RAAS, elevating Ang II levels, which directly contracts blood vessels and promotes sodium and water retention [113]. Ang II further aggravates oxidative stress, creating a vicious cycle. The concomitant metabolic disorders also contribute to elevated blood pressure

receptor tyrosine kinase activity, facilitate GLUT4 translocation, and improve glucose utilization in peripheral tissues [115, 116]. A cross-sectional study among Iranian women revealed a significant positive correlation between dietary magnesium intake and insulin sensitivity assessed via QUICKI (with QUICKI values of 0.34 ± 0.02, 0.36 ± 0.01, 0.40 ± 0.01, and 0.39 ± 0.02 for Q1-Q4 quartiles, respectively; P = 0.02). This association may be mediated by improvements in endothelial function, such as reduced sICAM-1 levels [117]. A large prospective cohort study in China (n = 5044) further found that maintaining serum magnesium concentrations within the range of 0.89–0.93 mmol/L could reduce the risk of insulin resistance (IR) by 29% (HR = 0.71, 95% CI 0.58–0.86) and significantly decrease the incidence of Type 2 diabetes. A pronounced nonlinear dose–response relationship was observed, suggesting that hypomagnesemia is an independent risk factor for the development of insulin resistance and diabetes [118].

There exists a complex bidirectional regulatory mechanism between magnesium deficiency and IR, which mutually promote each other, forming a vicious cycle of Type 2 diabetes and magnesium deficiency [108]. In pancreatic β-cells, magnesium ions regulate glucokinase activity and KATP channel function through the formation of Mg-ATP complexes, and their deficiency significantly inhibits insulin secretion. Simultaneously, impaired function of the magnesium-dependent transporter NIPAL1 further reduces basal insulin secretion levels. In insulin target tissues, magnesium deficiency leads to peripheral IR through multiple mechanisms: reducing the affinity of insulin receptor tyrosine kinase for Mg-ATP, interfering with protein phosphorylation processes, and affecting the cAMP activation pathway, ultimately causing insulin receptor desensitization [119]. Furthermore, magnesium deficiency promotes the release of proinflammatory factors, inducing chronic inflammation and oxidative stress, which further exacerbate IR [120]. Experimental studies have shown that magnesium deficiency can reduce the efficiency of insulin-dependent glucose uptake in adipocytes by 50% [121]. In terms of glucose metabolism regulation, magnesium participates in regulating the activity of key enzymes in glycolysis (such as hexokinase and phosphofructokinase) and gluconeogenesis rate-limiting enzymes (such as PEPCK) through Mg-ATP complexes. Deficiency leads to increased PEPCK activity, promoting hepatic gluconeogenesis [122]. A study on Type 1 diabetic rats found that thiamine disulfide (TD) inhibits gluconeogenesis by regulating PEPCK gene expression, thereby improving IR and blood glucose levels [123]. Genetic studies have revealed that variations in magnesium transporter genes such as TRPM6/SLC41A1 and mutations in KATP channels are associated with the risk of type 2 diabetes [124]. It's worth noting that diabetic patients often have increased urinary magnesium excretion, and persistent hyperglycemia can impair renal tubular magnesium reabsorption function [125], forming a vicious cycle that exacerbates hypomagnesemia [126].

IR is significantly associated with the risk of cardiovascular disease [127, 128]. The clinically used metabolic score for insulin resistance (METS-IR) is positively correlated with the risk of hypertension. For every 1-unit increase in the score, the risk of HTN increases by 3% (OR = 1.03, 95% CI 1.03–1.04) [129]. In the state of insulin resistance, hyperinsulinemia promotes the progression of hypertension by activating serum and glucocorticoid-inducible kinase 1 (SGK-1), which regulates the activity of vascular and renal sodium channels [130]. Studies have confirmed that hyperinsulinemia can enhance the activity of thiazide-sensitive Na^+-Cl^- cotransporter in the distal convoluted tubule, promoting sodium reabsorption through intracellular signaling pathways such as activation of mTOR complex 2 and stress-activated protein kinase/oxidative stress response kinase [131, 132]. It's important to note that this process relies on the phosphorylation of the Na^+-Cl^- cotransporter, which involves magnesium ions [133]. Hyperinsulinemia caused by insulin resistance promotes HTN through a dual mechanism: activating the sympathetic nervous system and the RAAS system, leading to vasoconstriction and water-sodium retention [134], on the other hand, magnesium deficiency exacerbates vasoconstriction by impairing insulin receptor tyrosine kinase activity and reducing vascular endothelial NO synthesis. Additionally, IR leads to increased levels of reactive nitrogen oxide species (RONS). When oxidative stress products exceed the body's antioxidant defense capabilities [135, 136]. they synergistically interact with magnesium ion antioxidant function defects, promoting the release of inflammatory factors, resulting in endothelial dysfunction and chronic low-grade inflammation, further impairing insulin sensitivity and vasodilation function[137].

Hypomagnesemia and metabolic syndrome

Metabolic syndrome (MetS) is a complex pathological state characterized by the clustering of multiple cardiovascular risk factors, including central obesity, glucose metabolism disorders, abnormal blood pressure, and dyslipidemia. This series of interrelated metabolic abnormalities significantly increases the risk of Type 2 diabetes and cardiovascular diseases, posing a major public health problem threatening the health of adults worldwide [136].Notably, each of these conditions has been linked to magnesium deficiency, and hypomagnesemia may trigger or exacerbate chronic low-grade inflammation, often

underlying the development of metabolic syndrome and its associated diseases [138].

Existing research evidence suggests a significant negative correlation between dietary magnesium intake and the risk of metabolic diseases [139]. The state of magnesium deficiency is closely associated with elevated levels of serum oxidized low-density lipoprotein (OX-LDL), further highlighting the crucial role of magnesium in maintaining normal lipid metabolism [140]. From a molecular perspective, magnesium ions play a vital role by regulating the gene expression of peroxisome proliferator-activated receptor gamma (PPARγ), a receptor that holds a central position in regulating processes such as cell apoptosis, differentiation, and the production of inflammatory cytokines. The underlying mechanism by which magnesium improves dyslipidemia may involve its regulatory effect on the activity of key enzymes involved in various lipoprotein metabolisms [141]. It is particularly noteworthy that magnesium deficiency can significantly enhance the activity of HMG-CoA reductase, thereby affecting the overall lipid profile and the balance of fatty acid metabolism [142]. Metabolic syndrome, characterized by lipid alterations, is highly prevalent among adults globally. Lipid droplets (LDs) accumulate in vascular endothelial cells in response to changes in triglyceride levels, potentially inducing vascular inflammation, promoting atherosclerosis, and causing hypertension by inhibiting NO formation, leading directly to cardiovascular disease [143]. Studies examining the complex nonlinear relationship between magnesium intake and hepatic fat accumulation have revealed potential hypertension-related differences [144]. A significant negative correlation exists between serum magnesium and fat mass, particularly among individuals without chronic diseases and who have adequate sleep [145]. Abnormal hepatic lipid accumulation can trigger nonalcoholic steatohepatitis (NASH), often accompanied by a range of comorbidities, including cardiovascular disease and insulin resistance. Magnesium deficiency is closely associated with the progression of NASH and the widespread triggering of its related complications [146]. A low magnesium environment appears to activate sphingolipid metabolism, which is intimately linked to metabolic disorders, cardiovascular disease, and other health issues [147, 148]. Additionally, sphingolipids serve as modulators of immune responses, and their impact on inflammation depends on specific molecules and the microenvironment [149]. Susceptibility to heart damage in hypertensive rats is associated with altered expression of sphingolipid metabolism enzymes [150]. Dietary magnesium content seems to influence the energy metabolism pathways of gut microbiota, such as oxidation or glycolysis. Fermentation of dietary fiber by bacteria in the colon forms short-chain fatty acids (SCFAs) [151]. Fibers with low MgO concentrations are more beneficial for gut bacteria to produce G6P, SCFAs, and lactic acid [152], and elevated SCFA levels offer protective effects against hypertension [153]. Improved magnesium utilization can increase the amount of medium-chain fatty acids (MCFAs) entering the circulation and lower plasma sucrose content [154]. Both short-chain and medium-chain saturated fatty acids may have potential benefits for cardiovascular health [155]. Future multi-omics studies may reveal how changes in bacterial metabolites affect intestinal magnesium absorption, providing a potential biological explanation for the occurrence of hypomagnesemia in patients with hypertension and metabolic diseases.

Meta-analyses have confirmed that magnesium supplementation significantly reduces body mass index (BMI) in patients with metabolic syndrome [156]. Pathological obesity stands as a profound driving factor for hypertension and its target organ damage. The synergistic effects of obesity-related chronic low-grade inflammation and metabolic disorders not only promote the continuous elevation of blood pressure but also exacerbate renal injury through multiple mechanisms, ultimately leading to the refractory characteristics of hypertension. Specifically, the release of proinflammatory factors triggered by abnormal adipose tissue proliferation, insulin resistance, and the overactivation of the renin-angiotensin system collectively contribute to a vicious cycle of blood pressure dysregulation and aggravated renal damage [157]. Mineral disorders have been linked to obesity, and oxidative stress appears to be particularly pronounced in overweight individuals, which seems to be associated with magnesium deficiency [158, 159]. Obese individuals have lower levels of antioxidants and magnesium, making them more susceptible to cardiovascular disease [136].

It is important to emphasize that while not all obese individuals exhibit a pronounced proinflammatory state, long-term nutritional deficiencies such as inadequate magnesium intake may be significant factors triggering metabolic abnormalities. Therefore, maintaining magnesium homeostasis in the body has important clinical value for the prevention and treatment of metabolic syndrome and its associated diseases.

Hypomagnesemia and other conditions

Hypomagnesemia, a state of electrolyte imbalance, not only manifests as a deficiency of magnesium itself but may also trigger other electrolyte disturbances, including hypocalcemia, hypokalemia, metabolic alkalosis, and hypoparathyroidism. Magnesium plays a crucial role in maintaining electrolyte balance, primarily by regulating

the transport of sodium and potassium across cell membranes [1].

Patients with primary HTN typically have lower systemic magnesium levels compared to normotensive individuals, and there is a positive correlation between serum magnesium concentration, free magnesium concentration in red blood cells, and blood pressure reduction [63]. Besides directly influencing blood pressure, magnesium can indirectly affect it by modulating the handling of potassium and sodium. Differences in magnesium homeostasis may impact pathways such as WNK/SPAK/OSR1 by influencing systemic potassium variations. The signal transduction from WNK through SPAK/OSR1 to NCC/NKCC 2 is highly recursive and tightly regulated, thereby regulating salt and potassium balance as well as arterial pressure [160]. Magnesium plays a profound role in blood pressure regulation by modulating renal sodium and potassium balance. When the body experiences sodium retention, it can trigger a series of pathophysiological changes, including fluid retention and increased intravascular volume, ultimately leading to elevated blood pressure. Magnesium ions counteract this process through a dual mechanism: directly promoting urinary sodium excretion and maintaining the activity of sodium–potassium ATPase, thereby effectively preventing the occurrence and development of volume overload and HTN. This regulatory effect is particularly significant in the prevention and treatment of sodium-sensitive HTN [161].

The importance of magnesium for musculoskeletal health cannot be overlooked, especially in hypertensive patients who face a high risk of magnesium deficiency and muscle atrophy. Studies have observed a positive correlation between dietary magnesium intake and atypical skeletal index (ASMI), but there is no direct correlation between magnesium supplements and ASMI [162]. This finding underscores the uniqueness and significance of dietary magnesium sources, suggesting that obtaining sufficient magnesium from daily diet, rather than relying solely on supplements, may be a key factor in preventing skeletal muscle loss in hypertensive patients. Magnesium also plays a vital role in improving athletic performance. It can provide the energy required for muscular activity by enhancing the availability of glucose in muscles and blood. Additionally, magnesium may optimize muscle performance by influencing energy metabolism, promoting protein synthesis and turnover in muscles, which is crucial for maintaining muscle mass and function [162].

Patients with hypertensive crises exhibit unique characteristics of the magnesium-blood pressure relationship: serum magnesium levels are significantly positively correlated with systolic blood pressure (SBP), which contradicts the traditional understanding of magnesium's blood pressure-lowering mechanism [163]. This finding suggests that under the special pathophysiological state of hypertensive crises, magnesium may participate in blood pressure regulation through different pathways than usual. Considering that serum magnesium levels may affect blood pressure control during crises, it is recommended to include serum magnesium testing as a routine monitoring indicator in clinical practice. Future research urgently needs to clarify the molecular mechanism of the magnesium-blood pressure relationship during hypertensive crises, the dynamic changes of serum magnesium, and the potential value of magnesium regulation therapy in blood pressure management for such patients.

Hypomagnesemia and renal hypertension and eclampsia

In the pathogenesis of HTN associated with eclampsia and kidney disease, hypomagnesemia also plays a significant pathophysiological role. There is a close association between HTN and kidney disease. Renal function defects can elevate blood pressure, while HTN can contribute to the development and progression of chronic kidney disease, often occurring concomitantly with arterial hypertension [164]. Studies have identified the abnormal activation of the NLRP3 inflammasome as a key molecular mechanism in this process. Notably, animal experiments have demonstrated that a low-magnesium diet can induce an increase in systolic blood pressure and significantly enhance the activation of the NLRP3 inflammasome in renal dendritic cells, suggesting that magnesium deficiency may be a crucial initiating factor for hypertensive nephropathy [165].

Magnesium deficiency is a common issue at various stages of chronic kidney disease (CKD). The underlying mechanisms involve multiple factors: on one hand, mitochondrial dysfunction caused by lipotoxicity and modified lipoproteins can lead to renal tubular magnesium reabsorption disorders; on the other hand, there is a significant negative correlation between serum magnesium and the prevalence of Mets in CKD patients (OR 0.75, 95% CI 0.59–0.94) [166]. Metabolic disorders can further exacerbate intracellular magnesium depletion [167]. This vicious cycle not only harms the kidneys themselves but is also closely related to the high incidence of cardiovascular complications in CKD patients [168].

Hypomagnesemia may cause pathophysiological changes through various complex mechanisms, leading to multiple complications associated with CKD. Clinical observations have revealed that the primary cause of death in CKD patients is often related to cardiorenal syndrome, highlighting the importance of maintaining magnesium homeostasis [169]. Furthermore, the deficiency of TRPM7 kinase is closely associated with

hypomagnesemia and reduced intracellular magnesium concentrations, further increasing the sensitivity to cardiovascular and renal fibrosis. PTEN regulates cell growth/survival and controls glucose and fatty acid metabolism [170]. Cardiovascular and renal injury downregulates PPM1A and PTEN, along with the upregulation of associated smad3 and ERK1/2, processes that have been shown to be magnesium-sensitive. Therefore, TRPM7-magnesium plays a crucial protective role in aldosterone-induced cardiovascular effects [70].

The underlying pathophysiology of eclampsia is closely related to inflammatory responses, and an imbalance in the ratio of M1 to M2 macrophages within the uterine microenvironment has been linked to various pregnancy complications [171]. Endothelial dysfunction is a central aspect of this disease, and platelet-activating factor (PAF) is involved in this process by promoting endothelial cell migration and angiogenesis. It's worth noting that in preeclampsia, the concentration of Mg is reduced, further decreasing the inhibitory factor of PAF, increasing PAF concentration, and leading to increased PAF-mediated platelet aggregation, which further exacerbates hypertension[172]. The levels of COMT and 2-ME in the placenta of preeclampsia patients are significantly lower compared to those with normal blood pressure, emphasizing the potential protective role of COMT in cardiovascular diseases [107].

Epidemiological studies indicate that women of reproductive age (15–45 years) demonstrate a high prevalence of hypomagnesemia [173], with pregnant women being particularly susceptible. Magnesium deficiency during pregnancy not only jeopardizes maternal health but may also impair fetal development and significantly increase the risk of preterm birth. Notably, chronic magnesium deficiency may trigger abnormal uterine contractions, thereby exacerbating adverse pregnancy outcomes [174].

Conclusion and outlook

Magnesium supplements exhibit significant individualized potential in the treatment of hypertension, capable of reducing SBP by more than 2 mmHg [7]. For hypertensive patients with well-controlled or target blood pressure, oral magnesium supplements do not show a significant blood pressure-lowering effect. However, in patients with poorly controlled HTN, daily supplementation of ≥ 240 mg of magnesium can safely lower blood pressure levels; for hypertensive patients not receiving medication, a daily supplement of > 600 mg of magnesium is typically required to achieve a blood pressure-lowering effect. It's worth noting that for untreated patients, although a daily magnesium supplement of < 600 mg may not simultaneously reduce systolic and diastolic blood pressure, it can still safely improve other cardiovascular risk factors and avoid potential adverse effects of antihypertensive medications [175]. This effect is closely related to magnesium's ability to regulate vascular smooth muscle calcium channels, improve endothelial function, and inhibit sympathetic nerve activity. Thiazide diuretics (TD) can have metabolic side effects, particularly the exacerbation of IR, which may paradoxically promote the progression of hypertension, creating a therapeutic contradiction. Combined supplementation with magnesium (such as magnesium citrate) can alleviate drug-induced hypomagnesemia and hyperglycemia. An optimized regimen of "potassium supplementation + magnesium supplementation + citrate" is more suitable for patients undergoing long-term TD treatment, especially in hypertensive populations with metabolic abnormalities [176].

Low serum magnesium levels are significantly associated with the risk of MetS, which includes HTN, hyperglycemia, and hyperlipidemia. Magnesium supplementation can exert pleiotropic effects by improving insulin sensitivity, regulating lipid metabolism, and reducing inflammatory markers such as C-reactive protein. The Qatar Biobank study further suggests that maintaining serum magnesium levels ≥ 0.83 mmol/L and a calcium-magnesium ratio ≤ 2.74 can reduce the risk of MetS [177]. The antioxidant properties of magnesium (such as reducing free radical damage) may delay the progression of atherosclerosis, thereby lowering the risk of cardiovascular events. Magnesium deficiency can exacerbate stress responses by activating the hypothalamus–pituitary–adrenal axis (HPA axis), promoting hypertension and neuropsychiatric symptoms such as anxiety [178]. Magnesium supplementation can improve gut-brain axis imbalances by regulating intestinal flora diversity (such as increasing short-chain fatty acid-producing bacteria) and stabilizing HPA axis function [179]. Promoting a magnesium-rich diet (such as whole grains, leafy green vegetables, and nuts) can serve as an economically effective primary preventive measure [180].

Future research should focus on elucidating the mechanism of action of Mg^{2+} transporters (such as TRPM6/7) in hypertension and the synergistic anti-aging effects of magnesium and Klotho protein on blood vessels. Large-scale RCTs are needed to establish standardized supplementation regimens (including dose and magnesium formulation optimization) for different populations (such as those with chronic kidney disease or obesity) [77, 181]. It is necessary to integrate microbiome-metabolomics techniques to reveal new targets for magnesium in regulating the gut-brain axis and conduct long-term follow-up studies to verify the improvement of hard endpoints such as cardiovascular mortality by magnesium supplementation (with an optimal serum magnesium threshold of 1.9–2.2 mg/dL) [182].

In conclusion, magnesium supplements have both therapeutic and preventive value in the comprehensive management of HTN and metabolic diseases. However, their clinical application requires individualized assessment (such as baseline magnesium status and comorbidities). Future interdisciplinary research is needed to facilitate the transition.

Symptoms/ Diseases	Effectiveness	Recommended dosage and formulation	Mechanism of action	References
Hypertension	2–3 mmHg ↓ in SBP, 1.78 mmHg ↓ in DBP	300–450 mg/day (magnesium citrate or magnesium glycinate)	Inhibits vascular calcium influx, modulates the RAAS system, enhances nitric oxide production	[13, 175] (Exhibits a U-shaped dose–response relationship)
Anxiety/ Depression	More effective for mild to moderate symptoms	200–400 mg/day (magnesium glycinate or magnesium L-threonate)	Stabilizes NMDA receptors, reduces neuronal excitability	[183, 184] (Requires combination with psychotherapy or medication)
Preeclampsia	May reduce risk (for high-risk pregnant women)	300–450 mg/day	Improves endothelial function, inhibits vasospasm	[185] (Requires evaluation, intravenous magnesium sulfate in acute phase)
Type 2 Diabetes Mellitus	Improves insulin sensitivity (HOMA-IR↓), lowers fasting blood glucose (high doses effective)	300-500 mg/day (magnesium oxide/magnesium citrate)	Enhances insulin receptor signaling, reduces oxidative stress, protects pancreatic beta-cell function	[186, 187] (Some cases show no effect on fasting blood glucose, further investigation needed)
Metabolic Syndrome	Improves lipid profile (TG ↓, HDL ↑), lowers blood pressure (2–3 mmHg ↓ in systolic blood pressure)	400–500 mg/day (mixed magnesium formulations)	Modulates lipid metabolic enzyme activity, inhibits vascular calcification, enhances NO-mediated vasodilation	[188] Requires long-term supplementation (≥ 3 months)

Abbreviations

HTN	Hypertension
OR	Odds ratio
RAAS	Renin–angiotensin–aldosterone system
TRPM6	Transient receptor potential melastatin 6
MDS	Magnesium depletion status
CVD	Cardiovascular disease
CKD	Chronic kidney disease
VSMC	Vascular smooth muscle cell
EDHF	Endothelium-derived hyperpolarizing factor
PH	Pulmonary hypertension
TJ	Tight junction
ZO	Zonas occlude
MYPT1	Myosin phosphatase target subunit 1
NMDA	N-methyl-D-aspartate
COMT	Catechol-O-methyltransferase
ME	2-Methoxy estradiol
AT1R	Angiotensin II type 1 receptor
SGK-1	Serum and glucocorticoid-regulated kinase 1
BMI	Body mass index
Mets	Metabolic syndrome
ASMI	Appendicular skeletal muscle mass index
SBP	Systolic blood pressure
PAF	Platelet-activating factor
HPA	Hypothalamic–pituitary–adrenal
DBP	Diastolic blood pressure

Author contributions

WLW: Conception, figure creation, and original draft writing; MG: Review and editing; PL: Review and editing; XZ: Supervision, guidance, review, and editing; HYY: Supervision and guidance; XG: Review.All authors reviewed the manuscript.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the General program of the National Natural Science Foundation of China (82370438). Dalian Medical University, Interdisciplinary Research Cooperation Project Team Funding of Abnormal Blood Pressure Regulation and Hypertension (JCHZ2023014).

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics Approval and consent to participate

Not applicable.

Consent for publication

Consent to publish has been received from all participants.

Competing interests

The authors declare no competing interests.

Received: 24 December 2024 Accepted: 30 May 2025
Published online: 16 June 2025

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