Magnesium and Blood Pressure: A Physiology-Based Approach

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Hypertension is an important public health challenge because of its high prevalence and strong association with cardiovascular disease and premature death. Hypertension is a major cause of CKD, is present in more than 80% of CKD patients, and contributes to CKD progression. Risk factors for hypertension include, but are not limited to, age, race, family history, obesity, physical inactivity, tobacco use, and inadequate intake of minerals such as calcium, potassium, and magnesium. Magnesium is the second most abundant intracellular cation in the human body and plays an important role in insulin and adenosine triphosphate metabolism. Low dietary magnesium intake has been associated with an increased risk of developing hypertension in prospective cohort studies. Moreover, clinical trials suggest that magnesium supplementation has blood pressure–lowering effects. In addition, emerging data reveal potential mechanisms by which magnesium may influence blood pressure. Here, we will review these mechanisms, using a physiology-based approach, focusing on the effects of magnesium on total peripheral resistance and cardiac output.

Key Words: Magnesium, Blood pressure, Hypertension, Mechanism, Physiology

INTRODUCTION

Hypertension is a global public health problem, being responsible for 12.8% of all deaths worldwide.[1] Hypertension is a major risk factor for stroke, myocardial infarction, peripheral artery disease, and other chronic diseases such as CKD. Conversely, hypertension is present in more than 80% of CKD patients, and it contributes to the progression of CKD towards ESRD.[2] Risk factors for hypertension include, but are not limited to, age, race, family history, obesity, physical inactivity, and tobacco use. Furthermore, high sodium and calcium intake, as well as low potassium and magnesium intake, has been linked with hypertension.[3]

Magnesium is the second most abundant intracellular cation in the human body and acts as a cofactor for more than 300 enzymes. During the last century, dietary magnesium intake in the US population has declined from ~500 mg/d to ~175-225 mg/d.[4] This alarming trend runs in parallel with the massive increase in prevalence of diabetes and hypertension, fueling the concept that there may be a relationship between magnesium deficiency and these cardiovascular risk factors. This has been further substantiated by the fact that magnesium plays an important role in many physiological processes in the body, such as insulin metabolism. Indeed, not surprisingly, magnesium deficiency has been linked with several cardiovascular risk factors, including diabetes and hypertension, and chronic diseases such as cardiovascular disease and CKD.[5]

Recently, several meta-analyses have summarized prospective cohort studies and randomized controlled trials, demonstrating an inverse relationship between magnesium intake and hypertension risk as well as a blood pressure (BP)–lowering effect of magnesium supplementation. Yet, data addressing the underlying mechanisms remain scarce.

The aim of this review is to summarize available data on the potential mechanisms linking magnesium with BP, using a physiology-based approach. We structure our analysis according to components of BP physiology, including cardiac output determined by the stroke volume and heart rate, and the total peripheral resistance, which depends on vascular structure and function. Using this approach, we aim to provide a mechanistic basis providing further support to the existing studies (which will be addressed briefly) positioning magnesium supplementation as a promising (adjunct) approach for the treatment of hypertension.

EPIDEMIOLOGICAL AND CLINICAL STUDIES

Epidemiological studies have shown an inverse relationship between magnesium and the risk of developing hypertension.[6-8] Such studies used dietary magnesium measured by questionnaires, circulating magnesium levels, or urinary magnesium excretion to assess the relationship between magnesium status and risk of hypertension. A recently published meta-analysis of prospective cohort studies (in total >180,000 participants of whom >20,000 developed hypertension) suggested an inverse relationship between dietary magnesium intake and risk of hypertension; a 100 mg/day increment in magnesium intake was associated with a 5% lower risk of hypertension.[9] Besides demonstrating associations between low dietary magnesium, assessed as a single nutrient, and hypertension risk, effects of dietary patterns on BP have also been studied.[10,11] For example, it has been shown that the Dietary Approaches to Stop Hypertension diet, which can be characterized by high fruit, vegetable, and low-fat dairy intake, can reduce BP.[12] Moreover, it was demonstrated

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that a higher Dietary Approaches to Stop Hypertension score was associated with a higher urinary magnesium excretion, suggesting that this diet is rich in magnesium.[13]

Han and others[9] also studied the relation between serum magnesium and hypertension and found that the association was borderline significant (relative risk = 0.91; 95% confidence interval: 0.80-1.02). This could probably be explained by the fact that serum magnesium poorly represents magnesium status, because only 1% over the total body magnesium content is present in the circulation, whereas the 99% resides in the intracellular compartment. In addition, magnesium homeostasis is regulated via the balance between intestinal absorption and kidney excretion. Thus, low circulating magnesium can be compensated by decreased urinary excretion or increased intestinal absorption. In line with these observations, we have studied the association between urinary magnesium excretion and risk of hypertension in a general population-based cohort.[14] We found that each 1-unit increment in ln-transformed urinary magnesium excretion was significantly associated with a 21% lower risk of hypertension, independent of several risk factors, including body mass index, smoking status, parental history of hypertension and alcohol consumption. However, no association between plasma magnesium and risk of hypertension was found and, moreover, plasma magnesium was weakly correlated with urinary magnesium excretion, further supporting the assumption that circulating magnesium less reliably reflects dietary magnesium intake.

CLINICAL SUMMARY

- Almost half of the US population does not meet the estimated average requirement of magnesium
- Prospective cohort studies and clinical trials suggest blood pressure (BP)–lowering effects of magnesium supplementation
- Underlying mechanisms whereby magnesium lowers BP might be explained by the possible actions of magnesium on cardiac output and total peripheral resistance, which are the 2 components of the BP

The effect of magnesium supplementation on BP has been studied in clinical trials since publication of a landmark trial in 1983.[15] In this trial, hypertensive patients receiving either magnesium supplements or potassium supplements were followed for 6 months. Nineteen out of the 20 patients showed a significant decrease in BP in the magnesium group, while in the potassium group, no significant differences were observed before and after 6 months. In the last decade, clinical trials showed overall small, but clinically relevant effects of magnesium on BP.[16,17] Moreover, the total daily dose of magnesium supplementation might be essential, because the meta-analysis of Kass and others[16] reported a more pronounced effect of magnesium supplementation on BP in a subgroup with a higher dose (>370 mg/d). More recently, a meta-analysis including 34 clinical trials found overall significant BP-lowering effects of magnesium.[18] Systolic and diastolic BP were significantly reduced (−2.00 and 1.78 mmHg, respectively) at a median dose of 368 mg/d. The effect of magnesium on BP has not only been observed in healthy and hypertensive subjects but also in subjects with insulin resistance, prediabetes and other chronic diseases.[19] In these high-risk populations, average systolic and diastolic BP reductions of 4.18 and 2.27 mmHg, respectively, have been noted, which might have clinically relevant effects on cardiovascular health outcomes.

POTENTIAL MECHANISMS

Although current evidence from both observational and intervention studies suggests beneficial effects of magnesium on BP, the potential underlying mechanisms remain partly unclear. Yet, emerging data from mechanistic studies revealed that magnesium influences several pathways that may improve vascular stiffness, reduce vascular resistance, and lower circulating volume (Fig 1). These beneficial effects on the physiological components of BP will be addressed in more detail in the following section.

Magnesium and Cardiac Output

Previous studies demonstrated the effects of magnesium on the cardiac output through inhibiting the renin angiotensin aldosterone system (RAAS), particularly its components angiotensin II and aldosterone. The RAAS plays a fundamental role in the physiology of BP and the pathophysiology of hypertension. It regulates blood volume, vascular resistance, cardiac output, and arterial pressure. Angiotensin II is a key effector hormone of the RAAS. Through promoting sodium retention and vasoconstriction, angiotensin II increases the effective circulating volume and thereby cardiac output. Aldosterone, which is stimulated by angiotensin II, also stimulates reabsorption of fluid and sodium and the excretion of potassium.[20] Several studies reported inverse relationships between magnesium and aldosterone production.[21-25] Atarashi and colleagues[21] found that magnesium infusion decreased aldosterone production. Later, they observed that magnesium counteracts angiotensin II, suggesting that magnesium indirectly inhibits the production of aldosterone.[22] In addition, a direct effect of magnesium on aldosterone production was reported in a study by another group.[23] In this study, angiotensin II levels were unchanged in magnesium-deficient rats compared to healthy animals, and magnesium supplementation did not affect angiotensin II levels in these rats. In contrast, aldosterone levels did change after magnesium supplementation, suggesting that magnesium affects aldosterone production independent of angiotensin II. In untreated hypertensive subjects, renin levels were negatively correlated with serum magnesium levels and positively correlated with serum calcium levels.[26] How magnesium might affect the actions of angiotensin II and production of aldosterone at the molecular level remains unknown. It has been suggested that the actions of angiotensin II are mediated by an increase in intracellular calcium,[27] and magnesium might decrease these intracellular calcium concentrations.[28] Also, magnesium might activate membrane-Na+K+-ATPase in cardiac muscle cells, resulting in