Magnesium and Progression of Chronic Kidney Disease: Benefits Beyond Cardiovascular Protection?

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Experimental and clinical studies have demonstrated that magnesium deficiency leads to hypertension, insulin resistance, and endothelial dysfunction, and is associated with an increased risk of cardiovascular events. Given that cardiovascular disease and CKD share similar risk factors, the low magnesium status may also contribute to CKD progression. In fact, lower serum magnesium levels and lower dietary magnesium intake are associated with an increased risk of incident CKD and progression to end-stage kidney disease. Because these associations are independent of traditional risk factors, other pathways might be involved in the relationship between magnesium deficiency and the risk of CKD progression. Recent evidence has shown that magnesium suppresses phosphate-induced vascular calcification. Magnesium impairs the crystallization of calcium phosphate—more specifically, the maturation of calciprotein particles. Considering that phosphate overload causes kidney damage, magnesium might counteract the phosphate toxicity to the kidney, as in the case of vascular calcification. This hypothesis is supported by an in vitro observation that magnesium alleviates proximal tubular cell injury induced by high phosphate. Potential usefulness of magnesium as a treatment option for phosphate toxicity in CKD should be further investigated by intervention studies.

Key Words: Magnesium, Chronic kidney disease, Mineral and bone disorders, Phosphate, Calciprotein particles

INTRODUCTION

Although there is plenty of evidence regarding beneficial effects of magnesium on human health,[1] this divalent cation has received little attention in the field of CKD. This is surprising, given that calcium and phosphate—both of which closely interact with magnesium in the body—are widely recognized as the major players in the mineral and bone disorders of CKD. However, an increasing number of clinical studies have been focusing on the implication of magnesium for the prognosis of patients with CKD and end-stage kidney disease (ESKD) (Fig 1).[2] This trend is largely related to the emerging evidence that magnesium is a potent inhibitor of vascular calcification, and that lower serum magnesium levels are associated with a higher risk of cardiovascular mortality (reviewed by Davenport and colleagues in this special issue). Moreover, several studies have suggested that the low magnesium status may aggravate the progression of CKD. In this review, we will summarize the evidence about the relationship between magnesium and CKD progression, and discuss putative mechanisms underlying the potential benefits of magnesium on renal prognosis.

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MAGNESIUM DEFICIENCY AND RISK FACTORS OF CKD

Magnesium deficiency could occur in patients with CKD and the non-CKD population. The major causes of magnesium deficiency are as follows: (1) low magnesium intake (eg, a typical Western diet low in vegetables, and high in processed and fast foods); (2) impaired gastrointestinal absorption (eg, CKD patients with vitamin D deficiency and use of proton pump inhibitors); and (3) enhanced urinary excretion (eg, drugs such as diuretics and insulin resistance).

Over the past few decades, population-based cohort studies have indicated that low magnesium status is associated with an increased risk of cardiovascular disease, along with hypertension, insulin resistance, and endothelial dysfunction, common risk factors of CKD. Hence, we first provide an overview of how magnesium relates to these diseases.

Hypertension

One of the most fundamental physiological functions of magnesium is to inhibit calcium influx into vascular smooth muscle cells by antagonizing voltage-dependent L-type calcium channels and capacitative calcium entry.[3,4] Therefore magnesium potentially reduces vascular tone and blood pressure levels. Moreover, magnesium decreases the expression of endothlin-1 and increases the production of prostacyclin and nitric oxide in endothelium, thus further contributing to the promotion of vasodilation.[5]

More than 20 years ago, the Health Professionals Follow-up study, which included a total of 30,681 men without atherosclerotic risk factors, showed that a dietary magnesium intake of <300 mg/d increases the risk of incident hypertension.[6] This finding was subsequently confirmed by a post hoc analysis of the Prevention of Renal and Vascular End-Stage Disease study, wherein an inverse dose-response relationship was observed between 24-hour

urine magnesium excretion and the risk of hypertension.[7] Although intervention studies conducted thus far included a small sample size and obtained inconclusive results, a meta-analysis of 22 trials ($n = 1173$) showed that magnesium supplementation reduces systolic blood pressure by 3 to 4 mm Hg and diastolic blood pressure by 2 to 3 mm Hg.[8] Notably, a greater efficacy was achieved in trials prescribing a higher magnesium dosage.

Insulin Resistance

Magnesium is an essential mineral for glucose metabolism as it serves as a cofactor for many key enzymes in the glycolytic pathway.[1] Magnesium is also required for insulin signaling such as phosphorylation of the insulin receptor tyrosine kinase, and hence, magnesium deficiency can lead to insulin resistance.[9] Conversely, patients with diabetes mellitus have a high risk for developing magnesium deficiency[10] presumably because magnesium reabsorption through transient receptor melastatin 6 (TRPM6) in the distal tubules, which is activated by insulin signaling, is impaired under insulin resistance.[11] Therefore, a vicious cycle exists between magnesium deficiency and insulin resistance.[12]

Dietary intake of magnesium is closely related to the risk of type 2 diabetes mellitus. A meta-analysis of 13 prospective cohort studies ($n = 536,318$) showed that the risk of incident type 2 diabetes mellitus was reduced by 14% with a 100 mg/d increase in the dietary magnesium intake[13]; this relationship was particularly pronounced among those with a higher body mass index. Although it is unclear whether magnesium is useful to patients who have already developed diabetes, a meta-analysis of double-blind randomized controlled trials of patients with type 2 diabetes showed that magnesium supplementation over 4 to 16 weeks significantly reduced the plasma glucose levels and increased the high-density lipoprotein cholesterol levels.[14]

CLINICAL SUMMARY

- Magnesium deficiency is known to be associated with hypertension, insulin resistance, and endothelial dysfunction, common risk factors that contribute to the progression of CKD.
- Lower serum magnesium levels are associated with an increased risk of both incident CKD and progression to end-stage kidney disease.
- The potential protective effect of magnesium on the progression of CKD may be partly derived from its counteracting property against phosphate toxicity.

Endothelial Dysfunction

Experimental studies elucidated protective effects of magnesium on endothelium. In vitro studies of endothelial cells showed that a low magnesium medium promotes oxidative stress and inflammation, and induces the expression of proatherothrombotic factors such as plasminogen activator inhibitor-1 and vascular cell adhesion molecule-1.[5] Inbred mice with intracellular magnesium deficiency showed impaired endothelial-dependent vasodilation and reduced endothelial nitric oxide synthase expressions.[15]

Several randomized trials have examined the impact of magnesium supplementation on endothelial function. Shechter and colleagues[16] studied 50 patients with stable coronary artery disease who were randomly assigned to either the magnesium group (365 mg/d of magnesium supplementation) or placebo group. After 6 months, the endothelium-dependent brachial artery flow-mediated vasodilation was significantly improved in the magnesium group. Moreover, magnesium supplementation restored exercise tolerance, as assessed via the treadmill test. This finding was confirmed by other trials of different patient groups, including elderly diabetic and hypertensive patients[17] and hypertensive women treated with diuretics.[18]

MAGNESIUM AND THE RISK OF CARDIOVASCULAR DISEASE

Consistent with the previously mentioned evidence indicating the protective effect of magnesium against proatherosclerotic risk factors, several cohort studies in the predominantly non-CKD population have found a close relationship between magnesium status and the risk of myocardial infarction, heart failure, and stroke. Meta-analyses have revealed that lower circulating and dietary magnesium levels are both associated with a higher risk of cardiovascular events.[19-21] The Framingham Offspring Study showed that lower serum magnesium levels are also associated with a higher incidence of atrial fibrillation.[22] A randomized double-blind trial of 79 patients with severe congestive heart failure (New York Heart Association functional classification Stage 4) examined the effect of magnesium orotate on patient prognosis.[23] In that study, the 1-year survival rate was found to be significantly improved in patients receiving magnesium (75.7%) compared with that in the patients receiving the placebo (51.6%). Taken together, magnesium supplementation may offer a prognostic benefit among patients with chronic heart failure.

MAGNESIUM DEFICIENCY AND PROGRESSION OF CKD–COHORT STUDIES

As there is a close association between magnesium deficiency and cardiovascular diseases, and given that cardiovascular disease and CKD share similar risk factors and etiologies, it is plausible that low magnesium also contributes to the progression of CKD.

Using the database of the Atherosclerosis Risk in Communities study, a large population-based cohort including 13,226 participants, Tin and colleagues[24] examined the longitudinal association between the serum magnesium levels and the risk of developing CKD and ESKD. During a median follow-up period of 21 years, they clearly showed a dose-response relationship between baseline serum magnesium levels and the risk of CKD and ESKD. Compared with patients with serum magnesium levels