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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Financial Disclosure: The authors declare that they have no relevant financial interests.

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1548-5595/$36.00

https://doi.org/10.1053/j.ackd.2017.11.001

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

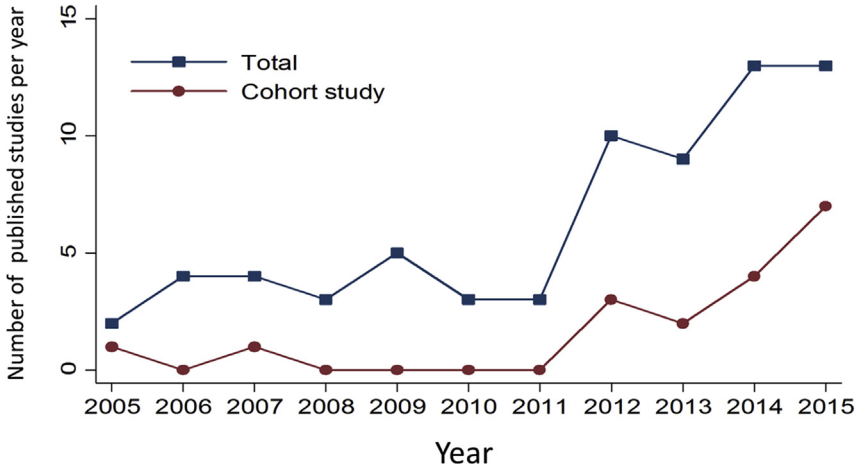

Figure 1. A rapid increase in the number of clinical studies regarding the role of magnesium in CKD. Adapted from Hamano and colleagues,[2] with permission of the Japanese Society of Nephrology.

of ≥0.9 mmol/L, those with serum magnesium levels of ≤0.7 mmol/L had a 1.58- and 2.39-fold higher risk of CKD and ESKD, respectively. This association was maintained after extensive adjustment for relevant clinical factors, including hypertension and diabetes mellitus, even when these factors were treated as time-varying covariates. This is the largest study in the general population that showed the relationship between serum magnesium levels and the risk of incident CKD and ESKD. In the Prevention of Renal and Vascular End-Stage Disease study, which included 5113 participants without CKD at baseline, Joosten and colleagues[25] additionally reported that the relationship between hypomagnesemia and the risk of incident CKD was maintained, even after adjustment for albuminuria.

A relationship between dietary magnesium intake and the risk of incident CKD was assessed in 2 independent cohort studies. The Healthy Aging in Neighborhoods of Diversity across the Life Span study, which enrolled 1252 city-dwelling African-American and Caucasian individuals with an estimated glomerular filtration rate (eGFR) of ≥60 mL/min/1.73 m^2, showed that a lower dietary intake (measured via 24-hour dietary recall) was associated with a rapid eGFR decline defined as ≥3% eGFR decline per year.[26] Another study—the Tehran Lipid and Glucose Study—found that dietary magnesium intake of >581 mg/d reduced the risk of incident CKD by approximately 60%.[27]

Because the significant association between magnesium and the risk of incident CKD, demonstrated by these studies, was independent of the traditional risk factors, there may be some other pathways that could explain the beneficial effect of magnesium on the kidney.

To assess the impact of magnesium on the progression of CKD, Van Laecke and colleagues[28] conducted a retrospective cohort study of 1650 patients with CKD, with a median follow-up of 5.1 years. In the multivariate analysis, they found that a 0.1 mg/dL increase in the serum magnesium levels was associated with a 7% decrease in the risk of death. Moreover, the eGFR declined more rapidly among patients with lower baseline serum magnesium levels. However, the significance of this association disappeared after adjusting for diuretic use in particular. As the serum magnesium levels and diuretic use were closely correlated, it may be somewhat difficult to demonstrate the effect of magnesium independent of diuretic use.

Because magnesium is closely involved in the pathogenesis of diabetes mellitus and its complications, we examined the relationship between the serum magnesium levels and the progression of diabetic kidney disease.[29] In this retrospective cohort study of a total of 144 patients with type 2 diabetic kidney disease, we observed that patients with serum magnesium levels of ≤1.8 mg/dL had a 2.12-fold higher risk of progression to ESKD than those with serum magnesium levels of >1.8 mg/dL after adjusting for baseline covariates including proteinuria and diuretic use. Similar results were reported by Pham and colleagues[30] who showed that lower serum magnesium levels were associated with a faster decline in kidney function determined by the slope of serum creatinine reciprocals versus time.

Therefore, magnesium deficiency increases the risk of not only cardiovascular disease but also kidney disease. It appears that the link between magnesium and CKD progression is more pronounced in patients with diabetes mellitus than in those without diabetes mellitus. Obviously, future intervention studies are needed to show the effects of magnesium supplementation on the renal prognosis of patients with CKD.

ROLE OF MAGNESIUM IN HIGH PHOSPHATE-INDUCED KIDNEY INJURY

Phosphate Toxicity to the Kidney

In addition to the traditional risk factors, there are several nontraditional factors that contribute to the progression of CKD. In particular, hyperphosphatemia may be directly harmful to the kidney. In animal models of CKD, a high phosphate diet aggravates kidney injury such as interstitial fibrosis, which is attenuated by the administration of phosphate binders.[31-35] Moreover, a study analyzing *klotho/NaPi2a*-double knockout mice demonstrated that

phosphate overload causes tubular cell apoptosis in the kidney.[36] Consistent with these animal studies, several, although not all, cohort studies showed an association between hyperphosphatemia and an increased risk of progression of CKD.[37-46] Notably, however, these studies have never taken into account the serum magnesium levels in their analysis.

Although the underlying mechanisms of how phosphate overload causes kidney injury remain unclear, Aihara and colleagues[47] showed that calcium phosphate crystals damage the proximal tubular cells by inducing oxidative stress. This is corresponding to the current concept that vascular calcification is caused by calciprotein particles (CPPs)—colloidal nanoparticles formed by a complex of calcium phosphate and several proteins such as fetuin-A.[48,49] An in vitro study showed that secondary CPPs (ie, matured CPPs wherein calcium phosphate aggregates are crystallized into hydroxyapatite), but not primary CPPs, strongly promote oxidative stress and calcification of vascular smooth muscle cells.[50] Secondary CPPs also enhance the production of inflammatory cytokines from macrophages[51] and aggravate intimal hyperplasia in an animal model of endothelial dysfunction.[52] Notably, CPPs were detected in the kidney tubular cells of patients with CKD.[53] It appears, therefore, plausible that the toxic effect of phosphate on the kidney is at least partly derived from the secondary CPPs in the tubular cells.[54]

Magnesium as an Inhibitor of CPPs Maturation

From the perspective of the mineral disorders in CKD, a critically important feature of magnesium is that it inhibits the crystallization of calcium phosphate.[55] This chemical property leads to its inhibitory effect on the maturation of CPPs. By measuring the transformation time of primary to secondary CPPs in the serum (T_{50}), Pasch and colleagues[56] provided striking evidence that magnesium prolonged T_{50} whereas phosphate shortened this value. Clinically, there is a positive correlation between serum magnesium levels and T_{50}, suggesting that circulating magnesium can suppress the maturation of CPPs.[57] Although limited by its small sample size, a recent randomized controlled trial of patients with CKD Stage 3 to 4 intriguingly found that magnesium supplementation dose-dependently prolonged the T_{50}.[58] Therefore, magnesium is considered to be a useful mineral to alleviate calcification stress in CKD. These findings provide a mechanistic insight into in vitro and in vivo observations that magnesium suppresses phosphate-induced vascular calcification.[59-68] We speculate that the extracellular role of magnesium to inhibit the maturation of CPPs contributes to the upstream mechanism of the anticalcification property of magnesium, although its intracellular role may also play a part.[63]

Magnesium-Phosphate Balance and Clinical Outcomes in CKD

Considering that magnesium counteracts phosphate-induced vascular calcification, magnesium might attenuate the cardiovascular risk associated with hyperphosphatemia. In a cohort of patients on hemodialysis, we found that the mortality risk associated with hyperphosphatemia was not increased among those with higher serum magnesium levels, whereas the risk was considerably increased among those with lower serum magnesium levels (Fig 2).[69] This result suggests the importance of magnesium-phosphate balance in the cardiovascular outcomes of patients on dialysis.

The ability of magnesium to alleviate phosphate toxicity might also be valuable in terms of phosphate-induced kidney injury. Here, we assessed the interaction between serum magnesium and phosphate levels on the risk of progression to ESKD in a retrospective cohort of 311 nondialysis patients with CKD.[70] The risk of ESKD was significantly increased among patients with higher phosphate and lower magnesium compared with the higher phosphate and higher magnesium group, suggesting that magnesium is protective against the risk of CKD progression derived from high phosphate. This notion is supported by an in vitro experiment showing that magnesium alleviates high phosphate-induced apoptosis and mitochondrial membrane depolarization of proximal tubular cells.[70]

Taken together, magnesium may serve as a therapeutic option for phosphate toxicity in terms of not only the cardiovascular risk but also the progression of CKD.

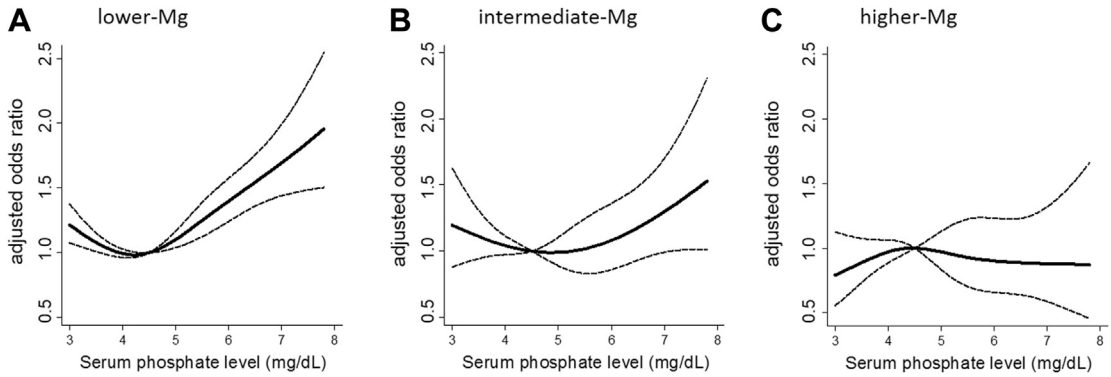

Figure 2. Interaction between serum magnesium and phosphate levels on the risk of cardiovascular death among patients undergoing hemodialysis. The adjusted odds ratio for cardiovascular mortality among patients with serum magnesium levels of (A) <2.7 mg/dL; (B) ≥2.7 and <3.1 mg/dL; and (C) ≥3.1 mg/dL. Reprinted from Sakaguchi and colleagues.[69]

HYPOMAGNESEMIA AND GRAFT FAILURE IN KIDNEY TRANSPLANT RECIPIENTS

Magnesium deficiency is common in kidney transplant recipients (reviewed by Cunningham J. in this special issue); in fact, more than 20% of patients suffer from hypomagnesemia after kidney transplantation, particularly among those receiving calcineurin inhibitors.[71] Notably, several studies have suggested that hypomagnesemia is associated with the development of complications in these patients, including new-onset diabetes mellitus after transplantation.[72,73] In addition, the low magnesium status may be involved in the progression of graft failure through enhancing the toxicity of cyclosporine. Animal studies have shown that magnesium deficiency exacerbates chronic cyclosporine nephrotoxicity.[74] In an observational study of 60 kidney transplant recipients with biopsy-proven chronic cyclosporine-induced kidney injury, patients with serum magnesium levels of <2 mg/dL had a 35% increased risk of graft loss compared with those with serum magnesium levels of ≥2 mg/dL.[75] Further intervention studies should assess whether magnesium supplementation is clinically effective for cyclosporine-induced kidney injury.

On the other hand, the detoxification potential of magnesium on phosphate toxicity, as discussed previously, may also be useful to improve the prognosis of graft survival. Keyzer and colleagues[57] reported that lower T_{50} was significantly associated with a higher risk of death-censored graft failure in a cohort of 699 kidney transplant recipients, thus suggesting that the increased calcification stress in these patients is unfavorable for graft function. As expected, the serum T_{50} of these patients was positively correlated with the serum magnesium levels. Therefore, magnesium supplementation may improve graft survival in part through an alleviation of calcification stress on the transplanted kidney.

CONCLUSIONS

As discussed, a number of experimental and observational studies have advocated the importance of magnesium in CKD. The major targets that magnesium acts on include not only the traditional atherosclerotic risk factors but also the calcification stress in CKD. The current clinical practice focuses on how to remove promoters of calcification stress, such as hyperphosphatemia and hypercalcemia. However, this therapeutic strategy is limited due to, for example, the side effects of phosphate binders and the malnutrition caused by dietary restriction. Hence, it is worth focusing on whether the increase in the calcification stress inhibitor, magnesium, can serve as an alternative strategy to yield better prognosis in patients with CKD. Further efforts are required to determine beneficial effects of magnesium for the progression of CKD.

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