Magnesium and Cardiovascular Disease in CKD: The Mysteries of a Humble Divalent Cation

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Despite its abundance, magnesium is an enigmatic electrolyte. Within the intracellular compartment, magnesium is the most abundant cation second only to potassium. Numerous biochemical processes, many of them essential for life, require magnesium as a cofactor.[1] However, magnesium remains underappreciated clinically, particularly in nephrology, because concentrations are monitored and treated only in specific disease states such as torsades de pointes or preeclampsia. However, there has been an increase in epidemiologic research investigating the relationship between serum magnesium levels and outcomes (specifically cardiovascular outcomes), bringing renewed attention to this often "forgotten" electrolyte.

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Patients with chronic kidney disease (CKD) often have abnormal serum magnesium levels, in part from decreased kidney clearance.[2] Serum magnesium accounts for only ~0.3% of total-body magnesium,[3] most of which is filtered by glomeruli. Approximately 15% to 20% of magnesium is reabsorbed by the proximal tubule. The specific mechanisms mediating this are not fully understood, and the absorption likely occurs by passive paracellular diffusion. The thick ascending limb is the primary site of magnesium reabsorption (~70%), again relying on paracellular reabsorption along a concentration gradient. Last, around 10% to 15% of magnesium is reabsorbed by the distal convoluted tubule through a channel complex of transient receptor potential cation channel subfamily M member 6 (TRPM6) and TRPM7 on the apical membrane.[3,4] The driving force for magnesium reabsorption in the distal convoluted tubule is the negative cellular potential primarily generated by potassium diffusion out through the Kv1.1 channel on the apical membrane. In addition to direct kidney handling, magnesium balance within the kidney often changes as a result of indirect effects of medications (such as loop or thiazide diuretics and calcineurin inhibitors), parathyroid hormone, volume status, electrolyte derangements, and serum magnesium levels.[4] Given the propensity for abnormal magnesium levels in patients with CKD, understanding how magnesium is regulated, as well as the implications of abnormal magnesium levels, is important.

Observational studies of patients with CKD have identified that both hypo- and hypermagnesemia are associated with poor outcomes.[5,6] Clinical trials of magnesium supplementation (aside from magnesium-phosphorus binders) are limited.[7,8] Overall, magnesium levels appear to be relevant, but with unknown significance, in patients with CKD.

With this in mind, the study by Negrea et al[9] in this issue of *Kidney Medicine* tested the association between serum magnesium levels with cardiovascular outcomes in patients with CKD.[9] To answer this question, the authors examined magnesium levels from the baseline visit in 3,867 participants enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study. The primary outcome was a composite of cardiovascular events (first incidence of heart failure, myocardial infarction, cerebrovascular accident, and peripheral artery disease) and all-cause mortality. Most notably, there was a U-shaped relationship in which magnesium levels < 1.9 and >2.1 mg/dL were associated with higher hazard for mortality and cardiovascular disease in unadjusted models. However, in models adjusting for demographic, clinical, and laboratory characteristics, the associations with primary outcomes were not statistically significant. Although not statistically significant in adjusted models, the findings are nonetheless intriguing and highlight that more research is needed to fully understand the role of magnesium on outcomes in patients with CKD.

Serum magnesium levels are a challenging exposure to work with in observational studies. Duly noted by the authors of the study, many factors can influence serum magnesium levels, including intestinal absorption, hormonal regulation, bone health, glomerular filtration rate (GFR), and medications.[4,10] The authors attempted to navigate these potential confounders by using the wealth of participant information contained within the CRIC Study to examine how they relate to serum magnesium levels in patients with CKD. Moreover, the study benefits from the rigorous data standards and close participant follow-up included in the CRIC Study. In total, this study provides a foundation for future research into the significance of magnesium in patients with CKD.

Despite these strengths of the study, several limitations should be recognized. Serum magnesium levels only modestly correspond with total-body magnesium stores and are difficult to interpret without data for dietary magnesium intake and excretion by the kidney. The study did not include dietary data or data for supplements. Several elements of this observational study suggest a noncausal relationship between serum magnesium levels and outcomes. For one, baseline magnesium levels were not lower in participants with use of medications that are typically associated with hypomagnesemia, including diuretics and proton pump inhibitors. Also, residual or unmeasured confounding is likely an issue in this study. For example, the positive association between higher

magnesium levels and risk is likely in part due to confounding by decreased estimated GFR. Finally, using repeat magnesium measurements over a shorter time frame might better define typical physiologic magnesium exposure, which is dynamic based on changes in daily excretion (eg, by the kidney or gastrointestinal system), diet, and medications.

The study by Negrea et al supplements the growing body of research studying magnesium with cardiovascular risk in patients with kidney failure. For example, higher serum magnesium levels have been found to be associated with reduced risk for cardiac arrhythmias in patients receiving dialysis.[11] Additionally, studies have investigated the plausible role of magnesium in decreasing arterial calcification. A recent randomized controlled trial of 57 patients with end-stage kidney disease (ESKD) examined the effect of using high-magnesium-containing dialysate to increase serum magnesium levels and serum calcification propensity (T_{50}; reflecting time to metabolize primary to secondary calciprotein, in which higher T_{50} represents lower vessel calcification propensity).[12] They found that using a higher magnesium concentration in the dialysate resulted in higher serum magnesium levels and T_{50}. However, whether this translates into reduced rates of cardiovascular disease in patients with ESKD is unknown.

There is a greater body of literature on the role of magnesium in cardiovascular disease in patients without CKD or ESKD. Efforts to study magnesium in cardiovascular disease stem from observations that (primarily) intracellular magnesium levels in the cardiovascular system reduce arterial tone, decrease blood pressure, and may have antifibrotic effects in the myocardium.[13]

In terms of outcomes, the evidence is mixed. Several epidemiologic studies demonstrated an increased risk for cardiovascular disease with lower serum magnesium levels, whereas others have noted a U-shaped relationship similar to what was seen in the study by Negrea et al.[14,15] Trials of magnesium supplementation in patients with heart failure have not demonstrated any benefit in terms of reduced mortality.[16] Moreover, among patients who received intraoperative magnesium during bypass surgery, investigators found that administration of magnesium was associated with a higher rate of postoperative atrial fibrillation regardless of serum magnesium values.[17]

Several hypotheses could explain the conflicting evidence for magnesium in cardiovascular disease. One possibility is that serum magnesium functions as a proxy for other causative mechanism (ie, sicker patients who require higher loop diuretic doses may become hypomagnesemic, or high magnesium levels may result from decreased GFRs, a documented risk factor for poor outcomes). The lack of a consistent trend between magnesium levels and cardiovascular disease may also reflect the disconnect between serum magnesium levels and intracellular magnesium concentrations within the myocardium.[18]

Moving forward, observational studies like the one from Negrea et al represent an important first step. They should not be taken as conclusive evidence for the benefit, or lack thereof, of magnesium for prognostication and/or treatment in patients with CKD. Future studies would benefit from more specific exposure measures. Most studies have examined the significance of serum magnesium, but it may be important to study intracellular magnesium, particularly across specific tissue beds or cell types. For example, 90% of total-body magnesium is stored in bone.[3] Data for magnesium intake and urinary excretion could be collected to characterize how magnesium supplementation changes total-body and intracellular stores (overall and organ specific) and serum concentrations. More detailed understanding of magnesium physiology in human studies may lay the foundation for clinical trials.

Furthermore, it is plausible that outcomes such as all-cause mortality or cardiovascular disease are too broad to truly understand the impact of magnesium levels in disease. Using more mechanism-based outcomes may generate relevant insights. For example, arterial calcium propensity represents a promising outcome measure to help understand how magnesium best fits into our current paradigm of mineral and bone disease in CKD. Additionally, sudden cardiac death and atrial fibrillation may function as outcomes in future studies because they are highly prevalent in patients with CKD and have supporting physiologic mechanisms linked to magnesium. Finally, given the role of magnesium in metabolism, metabolomic research might also identify other important biological processes that are affected by abnormal magnesium regulation.

In conclusion, the study by Negrea et al suggests that magnesium deserves more study in patients with kidney disease to untangle the relationship between magnesium and cardiovascular disease and determine whether magnesium regulation is important in preventing and treating cardiovascular disease in this population. With much to gain and little to lose, efforts should be taken to unlock the secrets of this humble divalent cation.

ARTICLE INFORMATION

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