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# Magnesium: An Important Orphan

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EDITORIAL

# Magnesium: An Important Orphan

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All parentless, Little Orphan Annie, Norma Jean (Marilyn Monroe, *c*. 1946), John Lennon, and George Herman ("Babe") Ruth were orphans, who despite humble upbringings became great success in their own right. In this issue of *Advances in Chronic Kidney Disease*, David Leehey and colleagues provide a platform for the magnificence of magnesium, whereas I focus on several germane, clinical aspects of our most treasured "orphan."

## INTRODUCTION

Magnesium has been termed the "orphan ion" because of its lack of specific endocrine control. However, this is not true because increases of aldosterone and parathyroid hormone activity, respectively, augment and lessen renal magnesium excretion. Nonetheless, among the bulk of nephrologists, magnesium has remained an orphan, primarily discussed as a treatment for unremitting, pre/eclamptic hypertension, or, as a nuisance, when elevated in patients with end-stage renal disease. Noteworthy is that nephrology's orphan ion participates in several hundred cellular biological processes daily, making it one of the most important minerals in humans, like iron. The popularity of magnesium and renal research regarding our orphan has surged since the description of paracellin-1,[1] the first magnesium-centric claudin. The mutation of paracellin-1 (claudin-16) is responsible for autosomal recessive familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC, MIM 248250). The purpose of this brief expose is to draw attention to a few major findings regarding this most important orphan ion.

## MAGNESIUM AND MORTALITY

Despite the ubiquity of magnesium in dietary sources that we should eat, many of us fall short of our nutritional need. Dietary surveys reveal that the recommended daily allowance for magnesium is not met in Europe and the United States.[2] Magnesium deficiency may impose risk for individuals with the metabolic syndrome, diabetes, and hypertension. The recommended daily allowance for men is 420 mg and for women 320 mg. Ingestion of nuts, seeds, legumes, whole-grain cereals, leafy vegetables, and water will suffice. That daily requirements for magnesium are not met is disturbing given the epidemiological information regarding serum magnesium levels and the risk of death.

Kieboom and colleagues recently published their findings in 2016 from an analysis of the prospective, population-based Rotterdam Study.[3] From data on 9820 participants (mean age 65.1 years, 56.8% female) followed for a median of 8.7 years, the association of serum magnesium levels and mortality was inverse. A 0.1 mmol/L (0.24 mg/dL) increment of this ion associated with a lower coronary heart disease risk (hazard ratio, 0.82; 95% confidence interval: 0.70–0.96). Low serum magnesium concentrations ($n = 431$) below 0.80 mmol/L (1.95 mg/dL) were also associated with increased coronary risk and sudden cardiac death ($n = 217$; hazard ratio, 1.54; 95% confidence interval: 1.12–2.11). Others reported similar findings. The 2013 meta-regression analysis of 532,979 participants by Qu and colleagues found that magnesium levels were inversely associated with risk for total cardiovascular disease events.[4] Only levels between 0.72 and 0.9 mmol/L (1.75–2.19 mg/dL) were significantly associated with adverse events.

Does the inverse association between magnesium concentration and death risk apply to chronic kidney disease (CKD) patients? It seems to. Kanbay and colleagues' review targets this question directly. They posit that low magnesium levels nurture a pernicious environment for accelerated atherosclerosis, cardiac dysrhythmia, and chronic myocardial ischemia.[5] Furthermore, the group advocates the use of magnesium carbonate as an intestinal phosphate binder treatment. The replacement of classical magnesium hydroxide by the carbonate congener yields a substrate for hepatic bicarbonate generation that is additionally less diarrheagenic. Furthermore, there is less chance of inducing hypercalcemia using a magnesium-based phosphorus binder. In hemodialysis patients, a magnesium-free dialysate can be used with magnesium carbonate to maintain magnesium levels in the normal range. This strategy may also reduce parathyroid hormone levels with a coincident decrease of serum


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calcium and phosphorus concentrations.[6] Conceivably, the reduction of parathyroid hormone, an independent risk factor for mortality in hemodialysis patients, would be beneficial.

## MAGNESIUM AND CALCIFICATION

Perhaps, the association of low magnesium levels in CKD patients[3,7,8] and increased cardiovascular mortality risk involves magnesium's ability to inhibit vascular calcification.[9] Vascular calcifications may appear in skin, muscles, blood vessels, and heart valves in advanced CKD. The process is complicated, and intensive, in vitro study provides a model. Vascular muscle cells transdifferentiate and assume a more osteoblast-like phenotype. The process is marked by new gene expressions of runt-related transcription factor 2 (*RUNX2*) and bone morphogenetic protein 2 (*BMP2*). Bone-specific alkaline phosphatase can now be secreted.

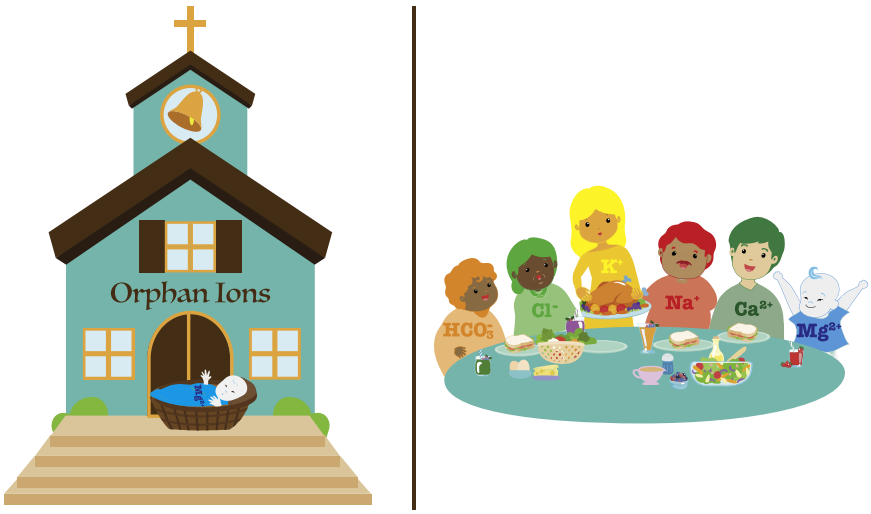
Consequently, the transdifferentiated vascular smooth muscle cells are no longer contractile, and can deposit mineral in the extracellular matrix. The deposition of calcium-phosphate nanocrystals is key, and the nanocrystals may participate in driving the process of transdifferentiation. Recall that the same process occurs in the progenitor sequence of idiopathic calcium oxalate lithiasis, i.e., Randall plaque formation.[9] Successive rounds of mineral deposition as nanocrystal in the surrounding matrix ultimately produce a metastatic calculus in soft tissue, a stiff vessel, or lithic heart valve. Extracellular magnesium ion can abrogate this calcification process via two mechanisms. First, magnesium ion directly suppresses transdifferentiation by reducing osteoblastic gene expression. Second, the nanocrystallization process is directly restrained by ionized, extracellular magnesium—simple chemistry at its best.[10] Interestingly, nanocrystallization is not inhibitable by selective chemical suppression of the vascular smooth muscle cells' magnesium channel, transient receptor potential cation channel subfamily M member 7 (TRPM7).[11]

Because advanced CKD patients are frequently exposed to proton pump inhibitors for a host of uremic gastrointestinal maladies, hypomagnesemia is likely more prevalent than suspected. No one needs reminding that this class of agents is among the most prescribed medications worldwide. Recently, chronic proton pump inhibitor use has been reported as a risk factor for incident CKD of the general US population, following analysis of data from the Atherosclerosis in Communities study with replication of findings using data from Geisinger Health.[12] Taken collectively, there is sufficient logic to maintain magnesium levels in advanced CKD patients and hemodialysis patients above the dangerous threshold levels associated with adverse cardiovascular outcomes. Prospective, randomized, controlled trials should only be conducted to determine the optimum level of serum magnesium concentration in CKD patients because an experimental group with lower-than-normal magnesium levels would be considered unethical by institutional review boards.

## MAGNESIUM IN DIABETES

Diabetic patients have lower serum magnesium levels,[13] which have been associated with poor glycemic control. Corsonello and colleagues determined that serum, ionized magnesium levels in 30 diabetic subjects (0.39 ± 0.06 mmol/L) were nearly 0.2 mmol/L less than the levels of 20 healthy control subjects (0.58 ± 0.05 mmol/L; $P < 0.001$).[14] Hypertriglyceridemia and hemoglobin A1c levels were significantly and inversely associated with the ionized magnesium concentration. Although not proven in this study, the hypothesis would be that enhanced urinary magnesium losses accounted for the lower serum levels. The kidneys are capable of high-level magnesium conservation during magnesium deprivation with hypomagnesemia. Just 5% of the ultrafilterable load of magnesium, amounting to 80–100 mmol daily, is excreted in urine daily. However, in the presence of an osmotic diuresis imposed by supervention of the tubular maximum for glucose reabsorption in an individual with poor glycemic control, net magnesium losses would accrue.

This observation is particularly important because magnesium, which is nearly completely intracellular, is



engaged in insulin action. In fact, insulin resistance in some persons may be attributed to low magnesium levels. Clinical studies have correlated reduced pancreatic beta cell activity with lower serum magnesium levels, reflective of total body magnesium depletion. Accordingly, magnesium supplementation improves glucose metabolism and insulin sensitivity.[3] The latter reflects myriad interactions of magnesium with multiple molecular pathways within the beta cell cytosol. Magnesium regulates glucokinase activity, adenosine triphosphate–sensitive potassium channels, and L-type calcium channels in beta cells. Hypomagnesemia also impairs the autotransphosphorylation of the insulin receptor, a reaction that is dependent on intracellular magnesium concentrations and critical to insulin action. Thus, hypomagnesemia impairs insulin secretion, ultimately interfering with beta cell depolarization and exocytosis of insulin.

Furthermore, peripheral nerve function and axonal degeneration may be responsive to magnesium repletion. Chu and colleagues demonstrated that a gradient of peripheral nerve dysfunction existed in type 2 diabetic individuals who had varying levels of hypomagnesemia.[15] Dividing serum total magnesium levels into tertiles of $<$0.85 mmol/L, 0.85–0.92 mmol/L, and $>$0.92 mmol/L revealed a gradient of nerve conduction abnormalities by composite Z scores of conduction velocities, latencies, and amplitudes. Overall, the worst nerve conduction parameters appeared in the lowest tertile of magnesium.

Thus, glycometabolic control begets glycometabolic control and complications vis-à-vis magnesium. The advocacy for "relaxed" glycated hemoglobins in diabetic kidney disease to prevent hypoglycemia may result in a greater frequency of hypomagnesemia if glucosuria becomes more frequent. Clinicians should measure serum magnesium levels periodically, particularly in uncontrolled diabetes.

## MAGNESIUM IN PREECLAMPSIA

Although nephrologists are not often summoned to the bedside of pregnant patients, they may be, especially if the patient has preeclampsia/eclampsia. Magnesium sulfate has been successfully used for decades to prevent eclampsia, lowering blood pressure, and preventing seizures.[16] Although multiple "standard" regimens exist and have been employed for the treatment of preeclampsia, it is notable that the mean steady-state concentration for total magnesium was only 4.84 ± 0.24 mg/dL. For ionized magnesium, it was 2.04 ± 0.14 mg/dL. This magnesium level is barely within the recommended range of treatment: total serum magnesium 4.2–8.4 mg/dL. Despite the low achieved magnesium concentration, seizures were prevented. Or were they?[17] The question is relevant because some contend that magnesium therapy for preeclampsia has not been shown salutary. Nonetheless, multiple clinical trials comparing magnesium therapy against benzodiazepines, phenytoin, and other antiseizure medications have demonstrated the superiority of magnesium.[17-20]

Serum calcium concentrations are essentially unaffected during magnesium infusions, implying the nonpathogenetic role of extracellular calcium in preeclampsia. However, vasodilation via relaxation of vascular smooth muscle cells likely occurs through alterations of intracellular calcium concentration. If magnesium decreased intracellular calcium, vasorelaxation would proceed through inactivation of the calmodulin-dependent myosin light chain kinase activity.[21] Experimental evidence has documented that magnesium serves as a vasodilator in vivo and in vitro. Large conduit and small muscular arteries exhibit magnesium-induced increases in diameter following exposure to higher magnesium environments, and skeletal muscles and the uterus relax. Eclampsia is considered a form of reversible posterior encephalopathy akin to hypertensive encephalopathy and is characterized by cerebrovascular vasospasm. Magnesium produces cerebral vasodilation, without alteration of cerebral blood flow,[16] leading to the conclusion that magnesium's efficacy resides in its ability to lower the systemic blood pressure. The effect of magnesium is pregnancy term-dependent, with reduced vascular magnesium-dependent vasodilation at term than in late gestation.[22] Despite the clinical success of magnesium in lowering blood pressure through vasodilation, the exact mechanism has remained elusive.

The same is true for the anticonvulsant activity of magnesium in preeclampsia. Eclampsia is associated with an enhanced, deleterious increased permeability of the blood-brain barrier.[23] Electroencephalograms delineate no changes during magnesium administration. However, this ion may restrict paracellular ion movement and decrease cerebral edema. At the endothelial level, an inhibition of actin stress fiber contraction via reduction in myosin light chain phosphorylation may play a significant role in the efficacy of magnesium-induced seizure prevention in eclampsia.[24-26] Another favorable mechanism may be inhibition of N-methyl-D-aspartate receptors, which when stimulated may induce seizures. At the astrocytic level, cerebral edema may be reduced by decreased expression of aquaporin-4 expression at the cells' endfeet. This water channel is expressed more during pregnancy.[27] In summary, the antagonistic effect on calcium by magnesium promotes peripheral vasorelaxation, thereby lowering the head pressure that begets cerebral blood flow. Vasogenic edema may be attenuated by magnesium through direct and indirect effects on astrocytes and tight junctions.

## MAGNESIUM IN HYPERTENSION

Hypertension in the general population may respond favorably to small amounts of dietary magnesium. Per a meta-analysis of randomized, double-blind, placebo-controlled trials by Zhang and colleagues, just 300 mg daily for 1 month may be sufficient to lower the systolic blood pressure by 2.00 mm Hg and the diastolic blood pressure by 1.78 mm Hg.[28] Magnesium is plentiful in whole grains, green leafy vegetables (iron is in there, too), and beans. Eating a balanced diet easily provides the threshold amount for efficacious downstream effects. However, magnesium's efficacy regarding blood pressure may only be accessible to magnesium-depleted individuals.

This nuance may explain the variability of results in trials of blood pressure reduction with magnesium, as delineated earlier by Houston[29] and Kass and colleagues.[30] Houston's hypothesis was that the magnesium-induced blood pressure reduction was more robust—about one-half of the response of one antihypertensive medication—with a blood pressure reduction of 5.6/2.8 mm Hg accompanying a daily intake of 500 mg of magnesium. Kass' meta-analysis evaluated 22 trials ($n = 1173$) with daily magnesium supplementation of 120 to 973 mg (mean dose, 410 mg). Combining all trial results demonstrates a 3–4/2–3 mm Hg systolic/diastolic blood pressure reduction within 3–24 weeks postintervention.[31] Supporting these data, Guerrero-Romero et al observed in a cross-sectional study of otherwise healthy Mexican children ($n = 3954$) that serum magnesium levels <1.8 mg/dL were associated with prehypertension and hypertension, defined as blood pressures exceeding the age range-specific 95th percentile.[32]

The importance of maintaining magnesium levels in hypertensive patients who are often diabetic should not be forgotten. Consequently, the use of potassium-sparing diuretics that also prevent diuretic-induced magnesuria should increase, especially since hypokalemia increases blood pressure modestly, even in normotensive individuals.[33] Potassium- and magnesium-sparing diuretics will prevent provocation of renal potassium-wasting via enhanced exodus of intracellular potassium through the renal outer medullary potassium channel.[34]

## SUMMARY

The orphan ion, magnesium, plays a vital role in human health and possibly an even greater role in cardiovascular and renal illness. Its fortuitous utility in pre/eclampsia has more scientific basis than ever. Lower magnesium levels are associated with impaired glycometabolic control, hypertension, and vascular calcification. These characteristics are present in abundance in CKD patients. A fundamental understanding of this orphan ion will make all nephrologists its parents.

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